THE AUSTRALIAN
NATIONAL
UNIVERSITY

RESEARCH SCHOOL
OF CHEMISTRY
INSTITUTE OF ADVANCED STUDIES

New Methods for Electrophilic Aromatic Halogenation

A thesis submitted in fulfilment of the
requirements for admission to the degree of

Master of Philosophy (Organic Chemistry)

By

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September 2003

In memory of Jaroslaw Dumanski

(21.11.1926 - 1.10.2002)

"All are lunatics, but he who can analyse his delusion is called a philosopher."

- *Ambrose Bierce*

"In theory, there is no difference between theory and practice. But, in practice, there is."

- *Jan L.A. Van de Snepscheut*

"Enough research will tend to support your theory."

- *Murphy's Law of Research*

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Author's Statement

The work described in this thesis is original and has not previously been submitted for a degree or diploma in this or any other University or Institution. To the best of my knowledge, this thesis does not contain material previously published or presented by another person, except where due reference is made in the text. Further, I give consent for a copy of my thesis to be deposited in the University library and be available for loan or photocopying.

Paul Gregory Dumanski

September 2003

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Chris Easton for all his guidance, supervision and lots of patience over the last three years. This thank you is also extended to fellow members of the Easton group in particular Adam Wright, Amy Philbrook, Brendon Barratt, Hideki Onagi, Ian Walker, Jamie Simpson, Leonie Chow, Lorna Barr and Marta Cieslinski for offering inspiration, friendship and help.

Thanks to everyone at the Research School of Chemistry who has helped me throughout my time here. A special mention must go to Chris Blake of the NMR staff who spent a lot of time and patience helping acquire data from the solvent suppression and 2D ROESY experiments. Also, thanks to Lorna Barr, Jamie Simpson and Adam Wright for proof reading parts of this thesis.

Thank you also to my parents and family for their continual support throughout the many years of my education. I must make a special mention with respect to my Father, Jaroslaw Dumanski who sadly passed away during the later stages of my degree. Also thankyou to my brother Peter for his friendship, support and for frequently bringing up many otherwise trivial topics to debate about.

Finally, thank you for your support and friendship to everyone outside the immediate work environment that I have been involved with since coming to Canberra. There are too many people to mention individually here; they include friends and teammates from soccer, people whom I regularly socialise with (you know who you are), my friends back in Melbourne and last but not least my girlfriend Lorna.

Abstract

Trifluorotoluene is shown to be a suitable replacement solvent for carbon tetrachloride for carrying out electrophilic aromatic chlorination. The use of novel catalytic groups to change the regioselectivity and increase the rate of aromatic chlorination in trifluorotoluene were investigated. The effects of cyclodextrins towards aromatic chlorination and bromination under aqueous conditions were also investigated.

Rapid intramolecular aromatic chlorination in trifluorotoluene was observed for a range of different phenylalkylamides and was attributed to neighbouring group participation by the amide group. Increases in the rate of aromatic chlorination of more than three orders of magnitude were observed for phenylbutyramide and phenylpropionamide compared to simple aromatics such as *t*-butylbenzene. The chlorination of amides in trifluorotoluene was found to be slightly faster than in carbon tetrachloride. Phenylalkylamines studied here all underwent aromatic chlorination in trifluorotoluene and showed good *ortho* selectivity. Phenylethylamine had the highest *ortho* selectivity, with the *o*/*p* ratio being 81/19.

The rate of aromatic chlorination of *t*-butylbenzene was increased at best by one order of magnitude by adding stoichiometric amounts of amide, which is thought to react here in an intermolecular fashion.

Cyclodextrins act as molecular reactors to change the ratio of products in chlorination and bromination reactions. For the aromatic chlorination of anisole and acetanilide, the *o*/*p* ratio changes in the presence of cyclodextrins to give predominantly the *para* isomer with α-cyclodextrin showing the greatest effect. Cyclodextrins also change the ratio of products of reactions of anisole, acetanilide, 3-methylanisole and 3-methylacetanilide with pyridinium dichlorobromate. With the mono-substituted aromatics, bromination is favoured at the *para* position over *ortho* substitution, and the effect is greatest with α-

cyclodextrin. In the reactions of the di-substituted aromatics, the cyclodextrins afford higher yields of the mono-brominated products and less of the di- and tribromides, and β-cyclodextrin has the most significant effect. These outcomes can be attributed to the inclusion of the substrates within the cyclodextrins restricting access of the reagent adjacent to the methoxy and acetamido groups.

Modified cyclodextrins (amino) retard the rate of aromatic chlorination but give predominantly the *para*-substituted isomer of anisole, and this can be attributed to the formation of *N*-chloro species at the amino group of the cyclodextrins.

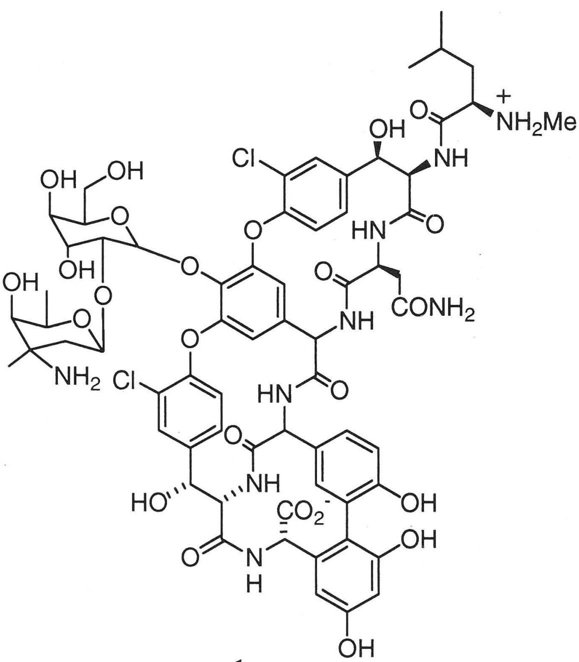
Chapter One

Introduction

The halogenation of organic compounds is a fundamental aspect of organic chemistry, because firstly, it is an elementary transformation and secondly, the halogenated products serve as important intermediates as the halo group can be converted efficiently into numerous other functionalities by simple chemical transformations.[1] The use of halogens such as chlorine and bromine and the manufacture of their respective organohalides has become a very contentious issue in the last few years, with conflicting claims and counter claims.[2] Much of the concern is about the impact these types of substances are having towards humans and the environment, because many organohalogens in the environment are persistent with a tendency to bioaccumulate due to high lipophilicity and chemical stability.[3-6] Quite astonishingly, better known organohalogens such as dioxin, PCB's, chlorophenols, chloroform and CFC's, once thought to result only from human activity have been found to occur naturally.[7] Not only are naturally occurring organohalogens ubiquitous in our environment, but concentrations of some of these chemicals exceed their anthropological levels.[8]

Organochlorine compounds in particular have received a lot of negative publicity from the general media and some environmental groups. The erroneous perception that all organochlorines are highly toxic and are found in the environment as a result of human activity clearly needs to be revised.[2] Presently there are more than 1600 known naturally occurring organochlorine compounds and new examples are continually being discovered.[9] Organochlorine compounds are produced naturally by volcanoes and forest fires but mainly by living organisms such as marine and terrestrial plants, bacteria, fungi, lichens, marine animals and some mammals.[9] In general, organochlorines are a diverse

group of compounds with a large range of vastly different physical, chemical and toxicological properties. While there are many organochlorines that are hazardous to human health and the environment such as DDT or some dioxins, there are many others that provide great benefit to society. For instance, approximately 85% of all pharmaceuticals either contain chlorine or use chlorine in their production.[10] Some examples include the drug vancomycin **(1)** which has been used as an antibiotic for more than forty years, diazepam **(2)** which is the active constituent of the tranquilizer valium and efavirenz **(3)** a new class of compound being used in clinical trials against HIV.[2,11]



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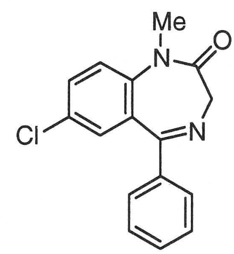

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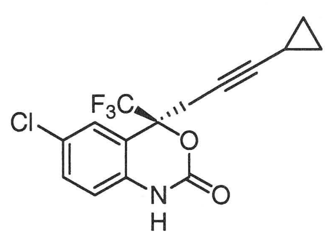

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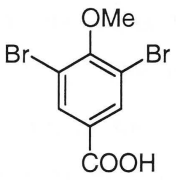
Organobromine compounds, once considered even more unusual than organochlorines, and also assumed to be highly toxic and solely synthetic pollutants, have also been found to be naturally occurring.[12] In fact, more than 1500 different types of organobromines can be attributed to natural sources.[13] Two examples of such compounds include dibromoanisic acid **(4)** found in marine sponges and avrainvilleol **(5)** a potent feeding deterrent found in marine plants. As was the case with organochlorines; organobromines are a diverse group of compounds, which include both compounds hazardous to humans and the environment as well as those with great benefits to society.



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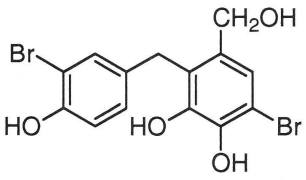

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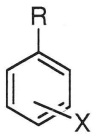
A class of compounds of particular interest and investigated herein this project are the halogenated aromatics **(6)**. They are of great importance due to their numerous applications, as fine chemicals for the synthesis of dyestuffs, disinfectants, polymers and fire retardants, and more importantly as intermediates for the synthesis of aryl organometallic reagents and bio-active compounds such as pharmaceuticals and pesticides.[14-16]



X = Cl, Br

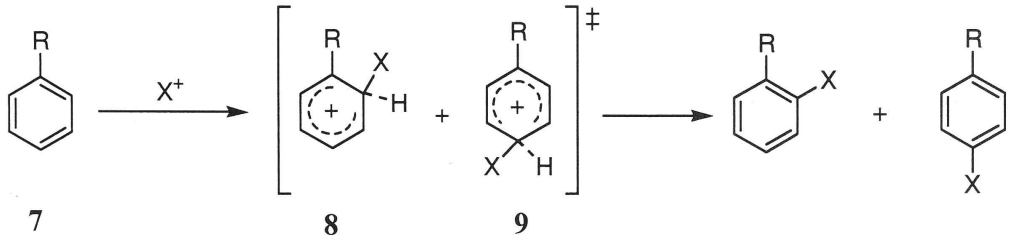
6

The responsible use and manufacture of organochlorine and organobromine compounds requires the ability to control the outcomes of the reactions with chlorinating and brominating agents, and avoid the formation of unwanted by-products. The aim of this project was to develop new and improved methods for halogenating aromatics in a more selective manner, under milder conditions than those normally required for such transformations.

Aromatic Halogenation

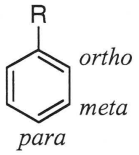
Halogenation is one of the most widely used and most extensively studied aromatic substitution reactions.[17] Halogenation is customarily brought about in one of three ways: with the use of molecular halogen e.g. Cl_2; with molecular halogen in the presence of a

Lewis acid catalyst; or with a halogen that is more positively charged than Cl_2, such as Cl^+ or $Cl{-}OH_2^+$.[18] The reactivity of the halogenating reagent increases when going up the halogen group in the periodic table from iodine to fluorine, hence chlorine is more reactive than bromine.[19] Aromatic compounds react with chlorine and bromine to give aryl halides *via* electrophilic substitution. The uncatalysed reactions follow simple second order kinetics and proceed *via* the formation of arenium ion intermediates such as **(8)** and **(9)**.[20] The mechanism of electrophilic aromatic substitution for an activated aromatic (R = activating substituent) involves two steps and is shown below (Scheme 1.1). The first step is reaction of the electrophile with the aromatic ring and formation of the arenium ion intermediates **(8)** and **(9)**. The second step is the elimination of a proton, which may occur spontaneously or involve participation of a base.[21] Some of the factors that affect the reactivity of aromatic compounds towards electrophiles include substituents on the aromatic rings, the nature of the electrophiles and the polarity of the solvents.[20,21]



Scheme 1.1

The inductive and resonance (or mesomeric) effects of substituents on the aromatic ring of mono-substituted benzenes strongly influence the reactivity of the position of substitution (*ortho*, *meta* and *para*).[18,21]



Inductive effects are dependent on the electronegativity and polarity of the bond of the substituent, and are transmitted through σ-bonds. Resonance effects arise from the ability

of substituents to donate or withdraw electrons from the aromatic ring through π-bonds.[18] The inductive and resonance effects of substituents have been quantified, based on the Hammett equation.[22] Table 1.1 shows a list of constants for σ_I (inductive effects of substituents) and σ_R^O (resonance effects of *para* substituents).

The values for σ_R^O are calculated for reactions *para* to the substituent, as the Hammett equation is not obeyed for *ortho* substitution of aromatics.[18] The descriptors +I and –I are used to indicate inductively donating and withdrawing groups respectively. Similarly +M and –M are used to describe resonance (or mesomeric) donating and withdrawing groups respectively. Alkyl groups, which do not have unshared electrons available for resonance, probably donate electron density *via* hyperconjugation.[20]

Table 1.1 σ_I and σ_R^O values for some common substituents[22]

Substituent	σ_I		σ_R^O	
t-Bu	-0.07	(+I)	-0.13	(+M)
Me	-0.05	(+I)	-0.10	(+M)
H	0		0	
CF_3	0.40	(-I)	0.08	(-M)
NH_2	0.12	(-I)	-0.48	(+M)
OH	0.25	(-I)	-0.43	(+M)
OMe	0.27	(-I)	-0.43	(+M)
CO_2Me	0.30	(-I)	0.20	(-M)
$CONH_2$	0.28	(-I)	0.08	(-M)
NHAc	0.20	(-I)	-0.30	(+M)
Cl	0.47	(-I)	-0.23	(+M)
Br	0.47	(-I)	-0.19	(+M)
NO_2	0.67	(-I)	0.15	(-M)
CH_2CO_2Me	0.10	(-I)	-	
$CH_2CH_2CO_2Me$	0.03	(-I)	-	

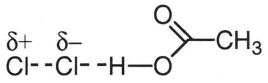
Inductive effects fall off rapidly with increasing distance from the ring.[18] This can clearly be seen in the decreasing σ_I value for the substituents CO_2Me, CH_2CO_2Me and $CH_2CH_2CO_2Me$ in Table 1.1. The σ_R^O values were not given for CH_2CO_2Me and $CH_2CH_2CO_2Me$ as the resonance effect of the ester group would not be transmitted through the alkyl chain due to the absence of π-orbitals.[18]

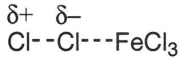
In the case of disubstituted benzenes, the substitution pattern is governed by the inductive and resonance effects discussed earlier, however, it is necessary to consider the additive effects of the two different substituents.[20] The directing effects of the two substituents may reinforce each other and make the outcome of reaction easy to predict. Conversely, when the substituents oppose each other, predictions become more difficult. In such cases the more activating substituent frequently has the dominating effect.[20]

The halogenation of reactive substrates, like phenol, aniline (where the +M effect is dominant) and polyalkylbenzenes (where both +I and +M effects contribute) proceeds readily in the absence of a catalyst.[20] For phenol and aniline the reaction leads to halogenation of all the available *ortho* and *para* positions. Halogenation of chlorobenzene, nitrobenzene and pyridine is much slower and requires more vigorous conditions such as high temperatures or concentrated acid.[19]

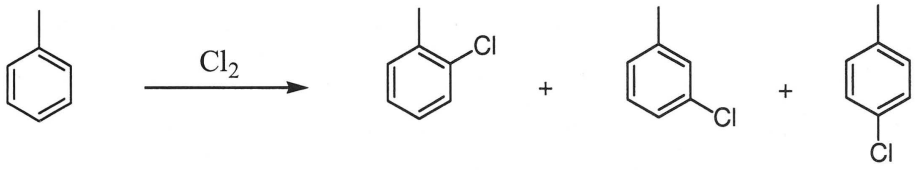
Aromatic chlorination

When molecular chlorine is used as the chlorinating agent it is frequently polarised by solvents such as acetic acid, or through the use of Lewis acid catalysts, to provide a more electrophilic source of chlorine. Such catalysts commonly include $AlCl_3$ and $FeCl_3$.[19] In non-polar solvents such as carbon tetrachloride, chlorine is not polarised by the solvent and the rate of electrophilic aromatic chlorination in the absence of catalysts is significantly slower.[23]





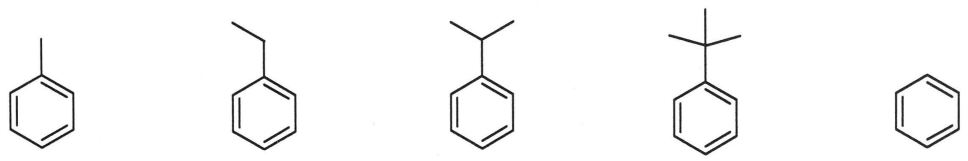
Mono-substituted alkylbenzenes react readily with chlorine in polar solvents, such as acetic acid, to give mixtures of predominantly *ortho* and *para* substituted products. Usually very little *meta* substitution occurs. For example the chlorination of toluene **(10)** gives the *ortho*, *meta* and *para* substituted products **(11-13)** with an isomer distribution ratio of 59.8/0.84/39.7.[19]



10 **11** **12** **13**

The electron withdrawing effect of a chlorine substituent has a sufficiently deactivating effect on the aromatic ring to limit further chlorination[19] and under relatively mild reaction conditions only monochlorination of alkylbenzenes occurs. Side chain halogenation will occur in reactions that are exposed to light.[18]

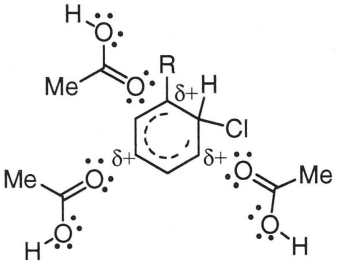
The general order of reactivity of alkylbenzenes in polar solvents decreases with increasing size of the alkyl groups.[18] The relative rates of aromatic chlorination of the monosubstituted alkylbenzenes **(10)**, **(14)**, **(15)** and **(16)** in acetic acid at 24 °C are 100, 84, 51 and 32 respectively.[24] Chlorination of benzene **(17)** is slower than that of alkylbenzenes, which are activated by the inductive effect of the alkyl substituents. The relative reactivity of benzene compared with the series above is 0.29.[24]

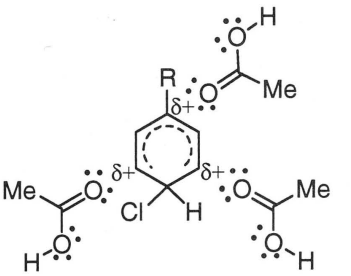


10 **14** **15** **16** **17**

The order of reactivity of the mono-substituted alkylbenzenes **(10)**, **(14)**, **(15)** and **(16)** is the reverse of that expected from the inductive effects of the alkyl groups which increase with chain branching.[18] The Hammett substituent constants for pure inductive effects (σ_I) of Me and *t*-Bu groups are –0.05 and –0.07 respectively.[22] This reversal of the inductive effect was first noted by Baker and Nathan[25] and has since become known as the Baker-Nathan effect. Several decades ago the reactivity of the monosubstituted alkylbenezenes **(10)**, **(14)**, **(15)** and **(16)** was thought to be due to hyperconjugation from the C-H σ bonds in the alkyl group donating electron density into the π-system of the aromatic ring. The effect of C-H hyperconjugation was predicted to decrease with increasing replacement of hydrogens on the carbon adjacent to the ring.[25] A major flaw with this theory was thought to be the assumption that C-H hyperconjugation would be more important than C-C hyperconjugation but that assumption is now known to be correct.{Taylor, 1990 #137;Cieplak, 1999 #369} The order of hyperconjugative electron release of alkyl groups has been shown to be the same as the inductive effect by measurement in the gas phase, where the order of reactivity of alkylbenzenes was the opposite of the Baker-Nathan order observed in solution.[18,26,27]

The decrease in reactivity of alkylbenzenes in electrophilic substitution reactions with increasing size of the alkyl substituent is now attributed to the effect of steric hindrance to the solvation of the intermediate species.[28-30]





The usual methods for chlorination of aromatics lead in many cases to mixtures of regioisomers,[31] which constitutes a loss of material and a waste of time and energy.[1] Techniques used by chemists to control isomer distribution in electrophilic aromatic substitution have involved using different reagents, solvents, catalysts and temperatures.[32]

Further disadvantages associated with classical chlorinating methodologies include the necessity to use large excesses of chlorine gas,[33,34] which results in loss of chlorine, thereby presenting both an environmental and economic problem,[34] and the use of catalysts such as $AlCl_3$ or expensive transition metal based ones, which are destroyed during workup, producing corrosive by-products and presenting a disposal problem.[35,36] Traditional methods for chlorination of aromatics, such as the use of elemental chlorine in acetic acid are both tedious and messy.[37] Such methods require the use of large volumes of acetic acid which ultimately have to be removed either by evaporation or neutralisation and the acid may react with compounds containing acid labile functionalities.[37] Therefore there is considerable need to devise alternative reaction protocols that avoid such catalysts and solvents and minimise the use of large excesses of chlorine.

Reagents other than elemental chlorine that are used for aromatic chlorination include *N*-chlorosuccinimide,[38-41] hypochlorous acid,[42] *t*-butylhypochlorite[43-46] and sulfuryl chloride.[32,47-50] Sulfuryl chloride is a less reactive chlorinating agent than chlorine so it is only useful for more activated aromatics however the larger size affords greater *para* selectivity for monosubstituted benzenes.[32] Hypochlorous acid and *t*-butyl hypochlorite are also less reactive than chlorine however the advantage with *t*-butyl hypochlorite is that the by-product is not acidic.

In recent years quite a number of other chlorinating systems have been investigated which allow milder reaction conditions and lead to greater selectivity than conventional reagents. A number of chlorine containing organic compounds such as *N*,*N*-dichlorourethane **(18)**, dichloramine-T **(19)**, *N*-chlorosuccinimide and *t*-butylhypochlorite have been used to effect monochlorination in the presence of silica in carbon tetrachloride in relatively short reaction times.[37] The absence of hydrogen chloride as a by-product and the convenience of the reagents provides significant advantages.

18 **19**

The utility of *t*-butylhypochlorite can be improved dramatically to give very high *para* selectivity for chlorination of monosubstituted benzenes in the presence of zeolites. The *ortho* / *para* substitution ratio for aromatic chlorination of toluene **(10)** in this system was found to be 9 / 91.[51] The same authors reported high *ortho* selectivity (*ortho* / *para* > 5 / 1, sometimes 15 / 1) for chlorination of phenol using *N*-chloroamines in the presence of silica.[52] Unfortunately, phenols react very readily in this system and polychlorination is a problem. Highly selective *para* chlorination of activated aromatics with *N*-chloroamines in acidic media in the absence of silica has also been reported. One of the mechanisms proposed for this reaction is a charge transfer process involving a radical cationic aromatic species.[53-56] A similar chlorinating system where reaction of phenol with sulfuryl chloride is catalysed by the presence of amines in non-polar solvents is reported to give highly selective *ortho* chlorination. The authors[57] suggest that the mechanism of aromatic chlorination involves *in situ* formation of *N*-chloroamines.

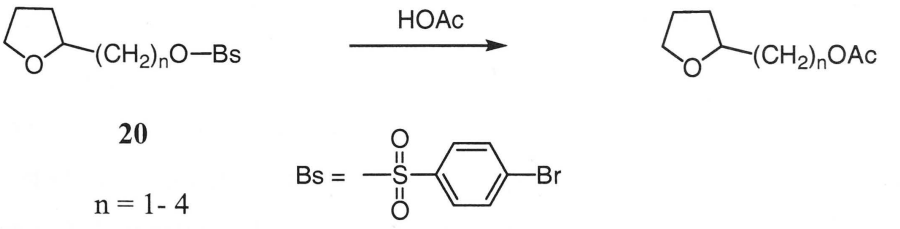
Metal chlorides of iron(III),[58] antimony(V),[58] vanadium(IV),[59] molybdenum(V)[59] and copper(II)[60] have been shown to chlorinate aromatic compounds without the involvement of molecular chlorine. This mechanism has been suggested to proceed *via* charge transfer and a radical cation intermediate.[59,61] Chlorination of aromatic compounds with metal halides is however sometimes accompanied by side chain reactions, which is a significant disadvantage.[33,59]

Other methods for chlorination of aromatics involve the oxidation of certain halides, for example, tin(IV) chloride in the presence of lead tetraacetate[33] and more recently, various metal chlorides in the presence of sodium bismuthate[62] appear to react *via* an ionic mechanism where molecular chlorine is generated *in situ*.[62] Similar methods have been reported where HOCl acts as the chlorinating agent and is generated *in situ* through the oxidation of hydrochloric acid or potassium chloride by various oxidants, such as

hydrogen peroxide,[1] sodium perborate,[34] sodium tungstate,[63] sodium metavanadate[63] and *m*-chloroperbenzoic acid.[64,65] Chlorination of aromatic compounds with halides under oxidising conditions frequently requires very drastic conditions and in many cases involves expensive oxidising agents, which are significant disadvantages.[62]

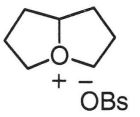
A study of aromatic chlorination on a broad range of aromatic compounds reported that aromatic compounds containing amine and amide functionalities could be chlorinated under mild conditions in non-polar solvents such as carbon tetrachloride, with elemental chlorine as the chlorinating agent in the absence of added catalysts *via* neighbouring participation.[23] Neighbouring group participation is a term which describes intramolecular reactions involving through space, non-electrostatic interactions within the same molecule.[66] Neighbouring group participation may lead to a product that is different to that expected in the absence of neighbouring group participation, for example, retention of configuration of a chiral carbon where inversion or racemisation would otherwise have been expected.[20] Other forms of neighbouring group participation are observed where participation leads to an enhancement of rate. In these circumstances the neighbouring group is said to provide *anchimeric assistance*.[66]

An example of neighbouring group participation providing anchimeric assistance is that of the tetrahydrofuran ring on the rates of solvolysis of 4-bromobenzenesulfonates in acetic acid (Scheme 1.2).[67,68] 2-Tetrahydrofuranalkyl 4-bromobenzenesulfonates **(20)** were found to undergo solvolysis at different rates depending on the lengths of the alkyl chains. The relative reactivities of the sulfonates **(20)** where n = 1-4 were found to be 1, 2, 2000 and 230 respectively.[67]



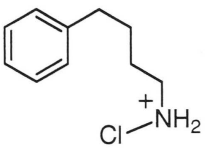
Scheme 1.2

The proposed intermediate responsible for the rapid solvolysis of the sulfonate **(20)** where n = 3 is the bicyclic oxonium ion **(21)** where the oxygen of the tetrahydrofuran group provides intramolecular nucleophilic participation and anchimeric assistance.[67]



21

Another example of neighbouring group participation providing anchimeric assistance is in the chlorination of certain types of aromatics with molecular chlorine in carbon tetrachloride. Significant increases in the rate of aromatic chlorination were achieved for compounds containing amine and amide functionalities, with some compounds showing an increase in rate of three orders of magnitude.[23] The proposed species responsible for the increase in the rate of aromatic chlorination were *N*-chloroamines such as **(22)** and *O*-chloroimidates such as **(23)**. This demonstrated how simple functional groups may be exploited, and allow reaction to occur in an intramolecular manner. So it could be said that the nitrogen from the amine **(22)** and the oxygen from the amide **(23)** are providing neighbouring group participation.



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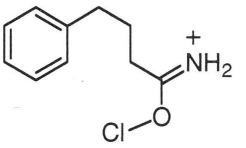
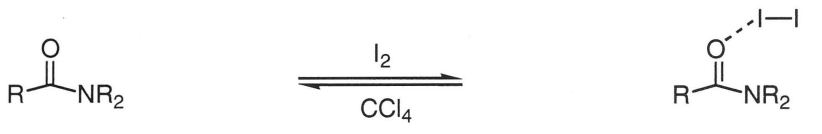


23

It has generally been accepted that halogenation reactions of nitrogenated compounds occur on the nitrogen.[69,70] In certain cases, for instance, amines, this is indeed the only reaction pathway possible. However, in the case of α-amino acids, there have been numerous studies on oxidation reactions with halogenating agents and there is contention as to whether halogenation takes place on the nitrogen of the amino group or the oxygen of the carboxylic group.[71-75] In the case of amides, a literature search revealed that studies by infrared spectroscopy of solutions of tertiary amides **(24)** and iodine in carbon

tetrachloride indicated that adducts are formed with molecular iodine complexed to the amides through oxygen **(25)** (Scheme 1.3).[76]



24 **25**

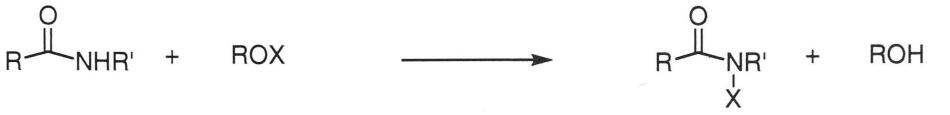
Scheme 1.3

Further examinations of the literature showed that molecular chlorine and bromine and their hypohalites also react with primary and secondary amides **(26)** and the characteristic products are *N*-haloamides **(27)** (Schemes 1.4 and 1.5).[77-79] The reactions with molecular halogen are reversible.

26 R' = H, alkyl, aryl **27**

X = Cl, Br

Scheme 1.4

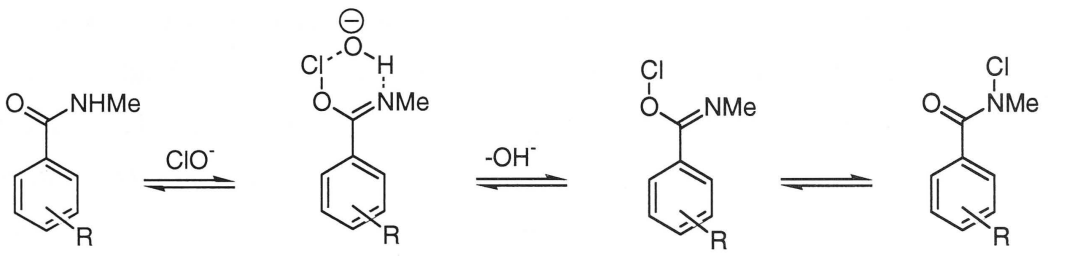


26 R' = H, alkyl, aryl **27**

X = Cl, Br

Scheme 1.5

Chlorination of *N*-methylbenzamides **(28)** with aqueous hypochlorous acid has been shown to involve an induction period and the initial formation of the *O*-chloroimidates **(29)** before rearrangement to the *N*-chloroamides **(30)** has been suggested (Scheme 1.6). This rearrangement of the *O*-chloroimidates **(29)** to the *N*-chloroamides **(30)** is reversible under alkaline conditions.[80]

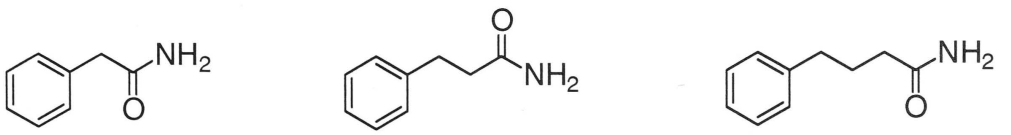


28 **29** **30**

Scheme 1.6

Based on what was known about reactions with amides and halogens it was considered possible that there was formation of an intermediate, most likely an *O*-chloroimidate or an *N*-chloroamide.

The amides that showed the most interesting effects in the particular study of aromatic chlorination in carbon tetrachloride[23] were phenylalkylamides with varying lengths of alkyl chain; more specifically they were phenylacetamide **(31)**, phenylpropionamide **(32)**, and phenylbutyramide **(33)**. The longer chained amides **(32)** and **(33)** showed significant increases in the rate of aromatic chlorination by three orders of magnitude, whereas phenylacetamide **(31)** showed less dramatic increases in rate.

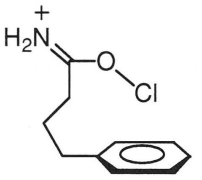


31 **32** **33**

It is also worth noting that when phenylpropionamide **(32)** was treated with chlorine in carbon tetrachloride, additional resonances in the ^{1}H NMR spectra of the reaction mixture were observed. This suggested that the relatively fast rate of aromatic chlorination of the amide **(32)** was related to the formation of an intermediate.

As discussed previously, the effect of polar solvents such as acetic acid is to increase the rate of aromatic chlorination by creating a more electrophilic source of chlorine and also

by providing stabilisation to benzenonium ion intermediates. It was envisaged that in non-polar solvents the amide group was providing some kind of intramolecular source of activated chlorine, such as through the complex **(34)**, or by stabilisation of the intermediated species, such as the benzenonium ion **(35)**. Such an intermediate as complex **(34)** could account for the increase in rate of chlorination for two reasons; firstly, there is formation of a more electrophilic source of chlorine than molecular chlorine, and secondly, the close proximity of the chlorinating species to the ring, allows intramolecular chlorination.



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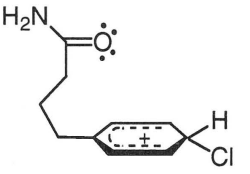
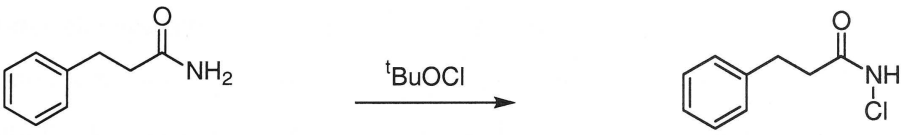


35

It is important to note that with previous studies on the *N*-chloro and *O*-chloro analogues of the amide **(32)** in carbon tetrachloride it was found that the resonances observed in ^{1}H NMR spectra were those due to only the *N*-chloroamide species.[23] This was best demonstrated by synthesising the *N*-chloroamide **(36)**, by reacting phenylpropionamide **(32)** with *t*-butyl hypochlorite (Scheme 1.7) and comparing ^{1}H NMR spectra of this to a mixture of phenylpropionamide **(32)** with chlorine in carbon tetrachloride at the very early stages of reaction. The ^{1}H NMR spectra looked almost identical and indicated that the species are probably the same. In another experiment to determine if the *N*-chloroamide **(36)** was responsible for the rapid aromatic chlorination of the amide **(32)**, a sample of the chloride **(36)** was left in carbon tetrachloride at room temperature in the dark. After five days no aromatic chlorination was observed by ^{1}H NMR. The absence of rearrangement suggested that while the chloride **(36)** was formed in the reaction, it was not the intermediate responsible for the rapid aromatic chlorination of phenylpropionamide **(32)**.



32 **36**

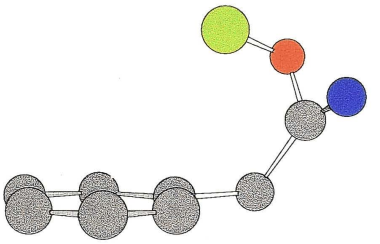
Scheme 1.7

Other observations included the fact that aromatic chlorination did not occur during *N*-chlorination of the amide **(32)** with *t*-butyl hypochlorite. This also strongly suggested that the intermediate responsible was not the *N*-chloroamide **(36)**. The intermediate responsible for the rapid chlorination of the amide **(32)** in carbon tetrachloride was through a process of systematic elimination divulged to be the protonated analogue **(37)** of the *O*-chloroimidate **(38)**.

37 **38**

It can be envisaged that for the intramolecular chlorination of the amide **(32)**, the better source of chlorinating agent would be the protonated *O*-chloroimidate **(37)** because the proposed mechanism would be much more plausible, whereas the resultant product for the chlorination *via* the *O*-chloroimidate **(38)** would leave a negative charge on the nitrogen. Other considerations to take into account are: the formation of the *O*-chloroimidate **(38)** must occur *via* an intermolecular exchange of the chlorine with the amide **(32)** rather than an intramolecular isomerization of the *N*-chloroamide **(36)**, and therefore require a significant concentration of the free amide **(32)**. The intermediate responsible for the rapid aromatic chlorination must only be present in trace amount as it is not apparent in the ^{1}H NMR spectra. Under the reaction conditions the amount of the complex **(38)** present would be dependent on the chlorine concentration, and this has been reported to be the case.[23]

The shorter chained amide **(31)** showed a less dramatic increase in the rate of aromatic chlorination compared to amides **(32)** and **(33)**. It was proposed that the aromatic chlorination of phenylacetamide **(31)** proceeded *via* the formation of an activated intermediate because firstly, the rate is about one order of magnitude faster than the rate of aromatic chlorination of simple alkylbenzenes such as toluene **(16)**. Despite this assumption, the rate of aromatic chlorination of phenylacetamide **(31)** is many times slower than those of the other amides **(32)** and **(33)** studied. Several possible explanations were considered for the difference in rate of aromatic chlorination of phenylacetamide **(31)** and the other amides **(32)** and **(33)**. If the mechanism of chlorination of phenylacetamide **(31)** in carbon tetrachloride is intramolecular, as suggested for the other amides **(32)** and **(33)**, then it is possible that chlorination is slower because the alkyl chain is too short to bend around and interact with the aromatic ring (shown by the representative *O*-chloroimidate species **(39)** in Figure 1.1) as efficiently as possible for the longer-chained amides **(32)** and **(33)**. For the same reason the reaction of the acetamide **(31)** may in fact be intermolecular.[23]

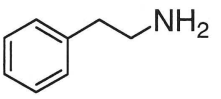


39

Figure 1.1 Chem3D™ representation of the *O*-chloroimidate species **(39)** formed from phenylacetamide **(31)**.

The *ortho* / *para* substitution ratio of 63/37 obtained for the aromatic chlorination of phenylacetamide **(31)** in carbon tetrachloride is lower than might be expected for an intramolecular reaction. This also suggests that the aromatic chlorination of phenylacetamide **(31)** in carbon tetrachloride occurs at least partly *via* an intermolecular mechanism which would not be expected to be as regioselective as an intramolecular mechanism.

In related studies, the amines **(40)**, **(41)** and **(42)** were treated with chlorine in carbon tetrachloride and the resultant mixtures of products were somewhat unusual and characteristic of neighbouring group participation.[23] Phenylethylamine **(40)** when treated with chlorine in carbon tetrachloride showed remarkable regioselectivity to give only the *ortho* chlorinated isomer. The selectivity towards the *ortho* isomer was suggested to occur through the formation of the *N*-chloroamine (*via* neighbouring group participation) and the fact that the alkyl chain was short enough to restrict the N-Cl complex from interacting with the *para* position.



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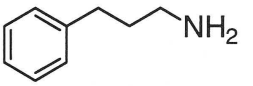

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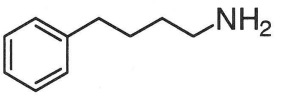


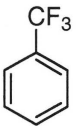
42

It was also noted that the longer chained amines **(41)** and **(42)** when treated with chlorine in carbon tetrachloride gave *ortho* / *para* ratios of 77 / 23 and 62 / 38 respectively.[23] This suggests that as the alkyl chain gets longer the isomer distribution for aromatic chlorination approaches the statistical norm. Aromatic chlorination in carbon tetrachloride was found to be relatively fast for the amines **(40)**, **(41)** and **(42)**, however rate constants could not be measured because there was rapid formation of HCl salts that formed heterogeneous mixtures.

It was found that when *O*-chloroimidate species were present in solution they could catalyse the intermolecular aromatic chlorination of other substrates. In a competing experiment, where toluene **(10)** was treated with phenylpropionamide **(32)** and chlorine in carbon tetrachloride the rate of aromatic chlorination of toluene increased by six times compared to reaction in the absence of the amide **(32)**. Related competition reactions are studied in this project.

The simplicity of the reaction system and the elegant use of amide and amine functional groups makes this a very efficient method for aromatic chlorination, however a distinct

disadvantage is that the reactions are performed in carbon tetrachloride. Some of the drawbacks associated with the use of carbon tetrachloride in general and more specifically as a reaction solvent include the high toxicity,[81-83] carcinogenic nature[84-86] and the ultimate phasing out of total use in the near future in accordance with the "Montreal Protocol".[82,87-91] One of the aims of this project was to examine alternative solvent systems that could be used as a suitable replacement for carbon tetrachloride. Such solvents need to be non-polar so that if any anchimeric assistance from neighbouring groups is occurring it will be more apparent, compared to polar solvents where anchimeric assistance might be obscured. Two such solvents chosen were α,α,α-trifluorotoluene **(43)** and α,α,α,α',α',α'-hexafluoroxylene **(44)**. Both solvents are industrially acceptable and are convenient solvents for the purpose of determining rate constants by NMR. They are strongly deactivated aromatics, so they would be expected to be inert to chlorination.



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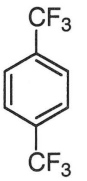
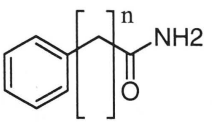
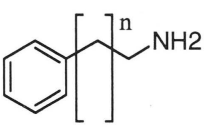


44

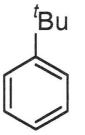
In the present work reactions of the phenylalkylamides **(31)**, **(32)** and **(33)** and the phenylalkylamines **(40)**, **(41)** and **(42)** were measured in trifluorotoluene **(43)** by ^{1}H NMR spectroscopy and compared to the aromatic chlorination of alkylbenzenes such as *t*-butylbenzene **(16)** which were reported to chlorinate slowly in non-polar solvents. These reactions were compared with chlorination of the aromatic compounds in carbon tetrachloride and acetic acid.



31 n = 1
32 = 2
33 = 3



40 n = 1
41 = 2
42 = 3



16

Reaction of an alkylbenzene with chlorine is a bimolecular reaction dependent on the concentrations of both the aromatic compound and of chlorine.[92] The rate is given by the second order rate equation, Equation 1.[93]

$$\text{Rate} = k[\text{A}][\text{Cl}_2] = -\frac{d[\text{A}]}{dt} = -\frac{d[\text{Cl}_2]}{dt} \qquad \textbf{Equation 1}$$

where [A] and [Cl_2] are the concentrations of aromatic compound and chlorine, t is time and k is the second order rate constant.

To determine the second order rate constant, the reactions were carried out with a large excess of chlorine to create pseudo-first order reaction conditions. Under pseudo-first order reaction conditions, where the concentration of chlorine is in great excess, the minute change in the concentration of chlorine due to reaction with the aromatic compounds can be ignored.

The rate of the pseudo-first order reaction is then dependent on the concentration of chlorine but independent of the small change in the concentration of chlorine due to aromatic chlorination. The rate of the pseudo-first order reaction is given by Equation 2.[93]

$$\text{Rate} = k'[\text{A}] = k[\text{A}][\text{Cl}_2] \quad \text{Because } k' = k[\text{Cl}_2] \text{ where } [\text{Cl}_2] \approx \text{constant} \qquad \textbf{Equation 2}$$

Integration of Equation 2 gives Equation 3.[93]

$$ln([\text{A}]/[\text{A}]_0) = k't \qquad \textbf{Equation 3}$$

where $[A]_0$ represents the initial concentration or the aromatic compound. The pseudo-first order rate constant k' is determined from the slope of the plot of $\ln([A]/[A]_0)$ against time. To obtain the second order rate constant k the pseudo-first order rate constant k' is divided by the concentration of chlorine (Equation 4).

$$k = \frac{k'}{[Cl_2]}$$ **Equation 4**

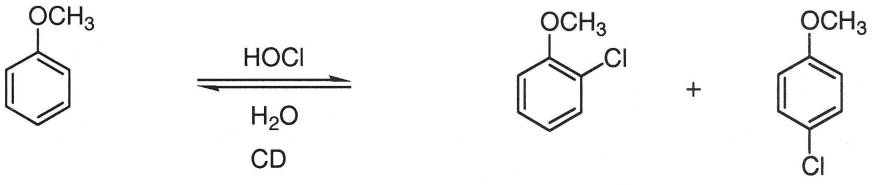
One of the aims of this project was to investigate new and improved methods for chlorinating aromatic compounds, by exploiting novel catalytic groups that are known to react in an intramolecular and intermolecular fashion in non-polar solvents that act as suitable replacements for carbon tetrachloride. Therefore a range of different aromatic amides and amines were chlorinated in trifluorotoluene. Work was extended to see if the highly labile *O*-chloroimidate intermediates could catalyse the chlorination of other aromatics present in the reaction mixture in an intermolecular manner and the results are reported in Chapter Two.

Water as a reaction medium

While there are potential advantages to using trifluorotoluene **(43)** as a reaction medium, there have been reports of aromatic halogenation performed in water. Water compared to other reaction solvents offers unsurpassed advantages.[94,95] Firstly, it is the cheapest solvent available (making many chemical processes more economical) and secondly, it is readily available, non-toxic, non-flammable and is an environmentally benign solvent.[96] There are other new and potentially *green* solvents being studied as potential replacements for conventional organic solvents such as ionic liquids[97] or supercritical carbon dioxide[98] however, they still present some limitations compared to water. Some of these include the susceptibility to degradation (into toxic components) when used above certain temperatures,[99,100] the low solubility for slightly polar compounds and lack of stability at atmospheric pressure.[98]

Breslow *et al.* demonstrated that anisole **(45)** could be selectively chlorinated in water by using hypochlorous acid in the presence of cyclodextrins.[101-104] In the absence of a cyclodextrin the chlorinated derivatives **(46)** and **(47)** of anisole **(45)** were formed in a

2:3 ratio. When the reactions were repeated with α- or β-cyclodextrin, substantially more of the *para* isomer **(47)** was formed, particularly in the case involving α-cyclodextrin where the ratio of the *ortho* isomer **(46)** to the *para* isomer **(47)** was 1:10.



45 **46** **47**

As discussed previously, most attempts to achieve site-selectivity in aromatic halogenation have been directed towards controlling the approach of the halogenating agent and the substrate.[53] These have included the use of bulky or micellar halogenating agents, or reactions in the presence of heterogeneous inorganic oxides and/or zeolites, however there have been very few reports on systems employing a complex between the halogenating agent and the substrate or the formation of host-guest complexes. Such systems as demonstrated by Breslow[102] possess several potential advantages such as having the halogenating agent in close proximity to the substrate thereby increasing the rate of reaction, and reducing the amount of halogenating agent required to near stoichiometric amounts. Furthermore, by having the substrate complexed by a bulky host there may be shielding of certain portions of the molecule from reaction and hence improvements to the regioselectivity. The effect of cyclodextrins on aromatic halogenation was investigated in this project.

Naturally occurring cyclodextrins are homochiral 1-4 linked cyclic oligomers of α-D-glucopyranose.[105] They are formed through the degradation of starch by the enzyme cyclodextrin glucosyl transferase.[106] Cyclodextrins were originally isolated by Villiers from the digest of potato starch by *Bacillus amylobacter*[107] and later characterised by Schardinger.[108,109] The most common of the series are the six, seven and eight membered homologues, being referred to as α-cyclodextrin **(48)**, β-cyclodextrin **(49)** and γ-cyclodextrin **(50)**, respectively.[110] Conformational restrictions cause these cyclodextrins to be toroidal in shape (Figure 1.2), with a hydrophilic exterior and a hydrophobic interior

cavity.[111] These properties of cyclodextrins make them well suited for the formation of water-soluble inclusion complexes of hydrophobic molecules.[112-114]

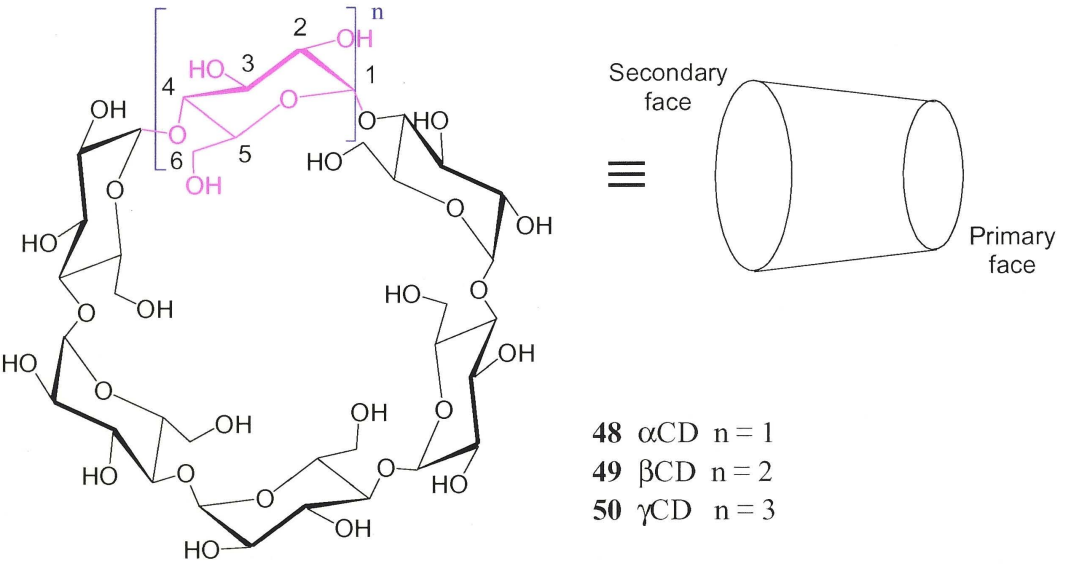


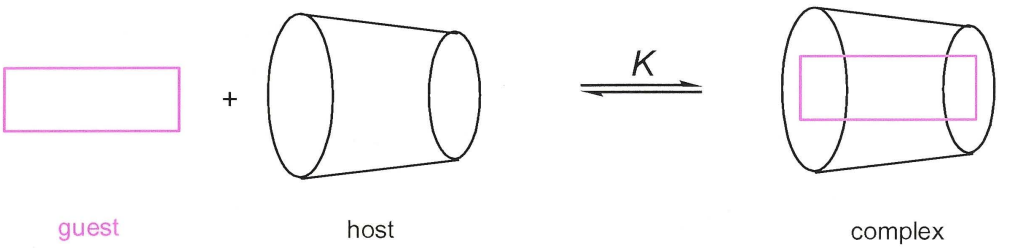
Figure 1.2 The structure of the three most common naturally occurring cyclodextrins.*

An inclusion complex is said to form when a molecule with a cavity, or capable of forming one (the host), encapsulates a smaller molecule (the guest) by purely non-covalent interactions.[113,115] These complexes can be thermodynamically quite stable and each is characterised by a thermodynamic stability constant or association constant (*K*) defined by the position of equilibrium between the host, the guest and the complex (Equation 5).[113,116] This is illustrated in Scheme 1.8 for the case where the host is a cyclodextrin. It should be noted that, as expressed below, *K* is a concentration stability constant rather than a true stability constant where activities of the equilibrium participants are employed instead of concentrations. Concentration stability constants are

* Cyclodextrins are commonly represented by truncated cones. When a substituent is shown on the narrow end, it represents a moiety that has replaced one of the C(6) primary hydroxyl groups, while a substituent shown on the wider end represents a moiety that has replaced either a C(2) or C(3) secondary hydroxyl group.

usually determined in solutions where a constant ionic strength is maintained by a supporting electrolyte.[114]

$$K = \frac{[\text{complex}]}{[\text{guest}].[\text{host}]} \qquad \textbf{Equation 5}$$



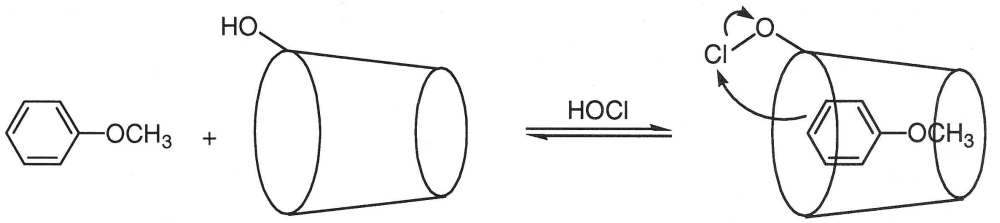
Scheme 1.8 The inclusion of a guest within a host (cyclodextrin) to form a complex.

The size, shape and nature of the guest involved will affect the stability of the complex and hence the value of the association constant.[113] The former two constraints are easily understood, as for the guest to include within the cavity, it must be able to be accommodated. On the first point, the more closely matched the size of the guest to the size of the cavity, the less distortion of the host occurs on inclusion and the more thermodynamically stable the resulting inclusion complex. This can be shown by the differing association constants between anisole **(45)** and α-cyclodextrin **(48)** and β-cyclodextrin **(49)** (whose annuli vary in size) where the values are 269 and 139 dm^3mol^{-1} respectively.[102,117]

Cyclodextrins have attracted considerable attention as enzyme mimics, due to their ability to form inclusion complexes with small organic molecules in water and catalyse reactions of the included species.[118-121] They have also been exploited as molecular reactors where they control the assembly of reactants to change the outcomes of chemical transformations.[101-103,122-132] Examples of the latter include the covalent attachment of dipolarophiles to cyclodextrins to reverse the regioselectivity of cycloadditions with

nitrile oxides[123,124] and the development of a urea-linked cyclodextrin dimer to bias competing reactions to give indigoid dyes.[125]

Probably the most straightforward examples of cyclodextrin molecular reactors are those that involve changes in the regioselectivity of reaction as a result of a substrate being included in such a way as to restrict access of a reagent, such as that shown by Breslow.[101-103] It was reasoned that, in the inclusion complexes with the cyclodextrins, the *ortho* positions of the anisole **(45)** are shielded from chlorination while the *para* position is still accessible. With this system it was suggested that the chlorination involves the formation of a hypochlorite **(51)** of a cyclodextrin hydroxyl group (Scheme 1.9), and consequently there is an enhancement in the rate of aromatic chlorination of anisole **(45)**.[101-103]

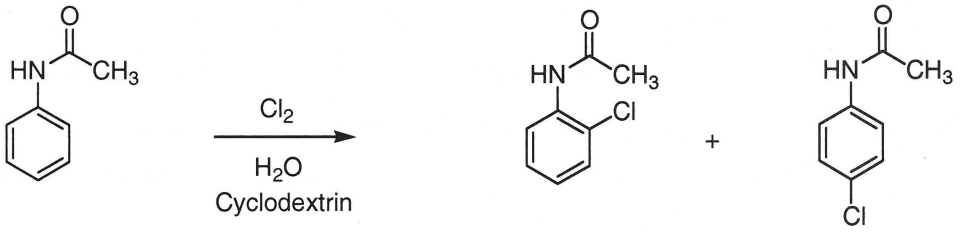


45 **48 or 49** **51**

Scheme 1.9 The proposed formation of the hypochlorite ester **(51)**.

In a related study of the chlorination of acetanilides using chlorine in water, Chênevert *et al.*[126] observed similar *para* selectivity for acetanilide **(52)** in the presence of α-cyclodextrin **(48)** and β-cyclodextrin **(49)** (Scheme 1.10), where the *o/p* product ratio of **(53)**/**(54)** was changed from 49/51 in the absence of a cyclodextrin to 10/90 and 40/60 with cyclodextrins **(48)** and **(49)** respectively. Less successful results were observed for benzanilides (where the *N*-acetyl group was replaced with an *N*-benzoyl group), where only slight improvements in *para* selectivity were observed (30/70 *o/p* at best) in the presence of cyclodextrins **(48)** and **(49)**. Chênevert discounted the involvement of the hypochlorite ester **(51)** in the chlorination of acetanilides contrary to Breslow[102] for

several reasons; firstly, no rate enhancement was observed for the particular system being studied,[126] and secondly, the formation of the hypochlorite ester **(51)** from a hydroxy group had an unfavourable equilibrium constant.[133]



52 **53** **54**

Scheme 1.10 The chlorination of acetanilide **(52)** to form the *ortho* **(53)** and *para* **(54)** substituted products.

Other examples of the use of cyclodextrins to influence aromatic substitution include that reported by Komiyama and Hirai,[127,128] where the regioselectivity of the Reimer-Tiemann reaction of phenol with chloroform was altered again in favour of *para* substitution. Similar results favouring *para* substitution were reported by de Rossi,[129] for the iodination of phenol in the presence cyclodextrins.

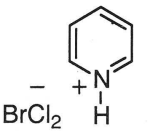
Tee and Bennett[134,135] investigated the effects of cyclodextrins on the bromination of anisole **(45)** with bromine/KBr in water. In this system the cyclodextrins did not alter the regioselectivity. Instead, the cyclodextrins retarded the rate of aromatic bromination which was suggested to occur firstly, due to the inclusion of both the substrate and brominating agent and secondly, due to the formation of a complex between the cyclodextrins and the tribromide ion.[134]

Generally, the usual methods for bromination of aromatics lead in many cases to mixtures of *ortho* and *para* regioisomers and/or polybrominated products,[15,18,136] which are undesirable for obvious reasons. At present there are a vast range of different brominating agents available to achieve aromatic bromination. The most simple reaction protocol

involves the use of molecular bromine, however this frequently requires the incorporation of a Lewis acid catalyst.[136] Some drawbacks associated with this reaction protocol include the sensitivity towards light and the hazardous nature of bromine vapour which is both toxic and irritating.[137] To overcome these types of problems, methods employing bromine have been improved over the years and bromination of aromatics is achieved under milder conditions, by employing bromine supported on zeolites,[138] silica/ clays,[139] Al_2O_3,[136] resins and *in situ* generation of *N*-bromoamines by using *n*-butyllithium with trimethyltin chloride and bromine.[15]

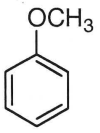
Due to the diverse range of reactivity of aromatic compounds, numerous methods have been reported in the literature for the electrophilic bromination of aromatics for example; using *N*-bromosuccinimide (NBS),[20,140] NBS in solid state reactions,[141] oxidative nuclear bromination using metal-oxo catalysts,[138] tungstophosphoric acid with cetyltrimethylammonium bromide[138] and the *in situ* generation of bromodimethysulfonium bromide.[142] In recent years there have been a number of solid brominating agents such as pyridinium tribromide ($PyHBr_3$),[143] $BDUHBr_3$,[144] Me_4NBr_3,[145] $PhMe_3NBr_3$[146] and Bu_4NBrCl_2.[147] All these brominating agents have the advantage that they are stable under ambient conditions making them easy to handle. Some disadvantages include low reactivity with some aromatics[147] (meaning large excesses of reagent are required), the necessity to use undesirable solvents such as carbon tetrachloride and the need to use complicated systems. In general there are very few brominating protocols that offer both a high regioselectivity and high reaction efficacy in environmentally benign solvents, such as water, and that may react at ambient temperature whist employing high substrate solubility.

Muathen *et al.*[147] recently showed that a range of aromatic compounds could be brominated with the use of pyridinium dichlorobromate ($PyHClBr_2$) **(55)** in aqueous methanol, however there was very little regioselectivity with monosubstituted aromatics.



55

The lack of regiocontrol for the aqueous bromination of aromatics and the recent account of the use of pyridinium dichlorobromate **(55)** prompted the investigation of the effect of cyclodextrins with this reagent. The substrates chosen for this study were, anisole **(45)** and acetanilide **(52)**, in order to make direct comparisons to the chlorination of these compounds. Phenyl acetate **(56)** was chosen on the basis that the ester is less reactive. The methyl-substituted anisole **(57)** and acetanilide **(58)** were also selected, firstly, on the basis that the ether and amide are more reactive towards aromatic substitution and secondly, this would allow an insight into the effect of cyclodextrins towards aromatic substitutions on more complicated systems. The effect of cyclodextrins towards these aromatic substitutions is reported in Chapter 3, together with studies of related aspects of aromatic halogenation.



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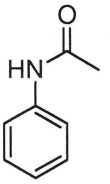

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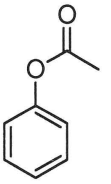

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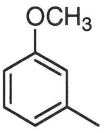

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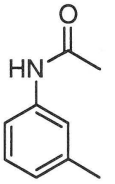

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Chapter Two

Aromatic Chlorination in Trifluorotoluene

As discussed in the Introduction, acetic acid in many cases serves as the solvent of choice for carrying out aromatic chlorination, due to the simplicity in the reaction protocol and the vast range of substrates that can be chlorinated, however certain drawbacks with such methods include: the necessity for large volumes of acetic acid to be used and the large excesses of chlorine required for such transformations.[36,37] Non-polar solvents such as carbon tetrachloride have been investigated and it was found that certain types of aromatic compounds may be chlorinated under mild conditions with only the use of elemental chlorine and in the absence of added catalyst *via* neighbouring group participation.[23] However, obvious drawbacks associated with such solvent systems include the high toxicity, carcinogenic nature and the ultimate phasing out of total use of carbon tetrachloride in the near future.[82,87,90] Therefore alternative solvent systems were investigated as a replacement for carbon tetrachloride.

Trifluorotoluene **(43)** was chosen for this purpose because it is suitably non-polar and chemically similar to carbon tetrachloride. Activating effects, such as intramolecular solvation, would be expected to be more apparent in trifluorotoluene than in a polar solvent such as acetic acid. In addition, trifluorotoluene is an industrially acceptable solvent and a strongly deactivated aromatic, and would be expected to be inert to electrophilic chlorination. To test whether this is the case, it was treated with chlorine in acetic acid for 24 hours and analysis of the mixture showed no traces of chlorinated products, thereby confirming the inert nature of the solvent. However, analysis of solutions of trifluorotoluene containing dissolved chlorine that had been exposed to light,

showed the presence of degradation products suggested to form *via* a radical mechanism. New resonances in the region of 4-5 ppm were observed and increased in intensity with exposure time (Figure 2.1), whilst the trifluorotoluene signals decreased. Therefore, care was taken to avoid any exposure of reaction mixtures to light.

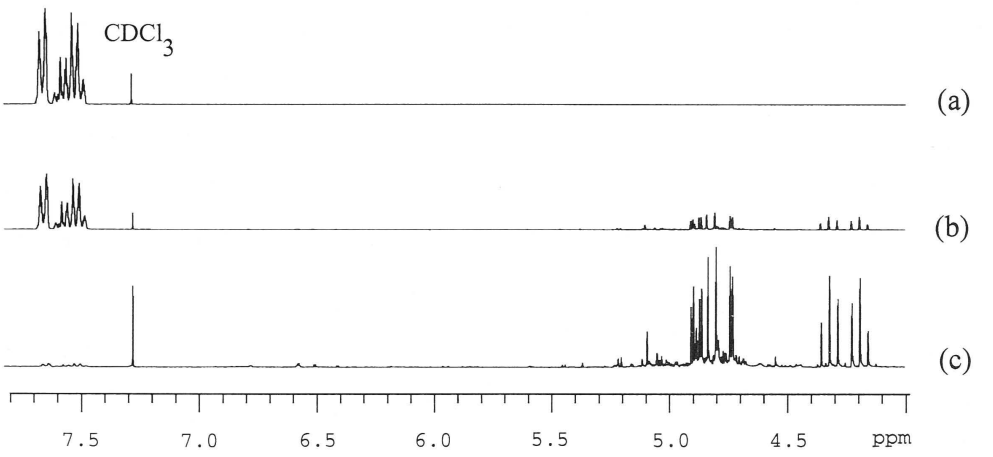


Figure 2.1 NMR spectra of (a) a trifluorotoluene solution, (b) a trifluorotoluene/Cl_2 solution left exposed to light for 24 hours, (c) a trifluorotoluene/Cl_2 solution left exposed to light for 7 days (spectra recorded in *d*-chloroform).

An alternative solvent considered was hexafluoroxylene **(44)**. This is a more strongly deactivated aromatic than trifluorotoluene and therefore it would be expected to be more resistant towards aromatic chlorination. The use of hexafluoroxylene was later deemed not necessary because reactions worked well in trifluorotoluene.

Experimental Method

In general, reaction rates were measured by integration of ^{1}H NMR spectra and samples were prepared by adding a chlorine solution of known concentration in trifluorotoluene to a known amount of aromatic compound. Reaction rates for aromatic chlorination of compounds **(33)** and **(32)** were measured by integration of methylene resonances in ^{1}H NMR spectra recorded at time intervals (900, 1800, 3600 and 7200 seconds) during reaction at 25 °C whereby the samples were purged with nitrogen to remove excess chlorine and solvent, then the residues were dissolved in *d*-chloroform. Compound **(31)** required longer times for reaction to occur and reaction mixtures were analysed on a daily basis for up to 1 week. A modification to the experimental method to determine the reaction rate for *t*-butylbenzene **(16)** and subsequent competition reactions was deemed necessary because the initial method discussed above was not successful. The major problem encountered was that during blow-down of reaction mixtures, significant amounts of *t*-butylbenzene **(16)** were lost due to the high volatility of this aromatic. The modified method involved running the NMR experiments in trifluorotoluene under solvent suppression conditions[148] (thereby minimising the background signal from solvent protons in NMR tubes). This was deemed necessary because the signals from the aromatic protons of trifluorotoluene would swamp the remainder of the spectrum, making it impractical to quantify reaction mixtures by integration. The NMR tubes were sealed with RotoTite® valves to prevent the loss of chlorine from solution and had a capillary insert present containing acetic acid-d_4 to provide an NMR lock signal and reference. The resonance due to residual acetic acid was calibrated against a solution of 5% TMS in trifluorotoluene and set to 2.69 ppm, to account for the difference in the bulk susceptibility of the capillary with respect to the sample.[149] Significantly longer reaction times were required for *t*-butylbenzene **(16)** because of the slower rate of reaction in trifluorotoluene. Because the rate of aromatic chlorination was slow ^{1}H NMR spectra were recorded at the start of reaction and then again after several days to determine extent of reaction. All samples were prepared in a darkened room, with only just enough light to see by, and carefully kept away from light until analysed.

The concentration of chlorine was measured by UV visible spectroscopy each time a new series of experiments was performed.[150,151] Stock solutions of chlorine were prepared by bubbling chlorine gas through the solvent, then determining the concentration of chlorine from the UV absorbance of a 1 mm sample at 380 nm. The 1 mm path length was used to obtain a workable absorbance range. The wavelength used was at 380 nm, which was not at the maximum absorbance for chlorine solutions; again this was done to reduce the absorbance to a workable range for the absorbance used. A calibration graph for the UV response to chlorine concentration was prepared by measuring the absorbance of a set of standard solutions at 380 nm. The concentration of chlorine in the standard solutions was determined by iodometric titration, then back titrating with standard thiosulfate solution (see below) whilst using starch as an indicator.[152]

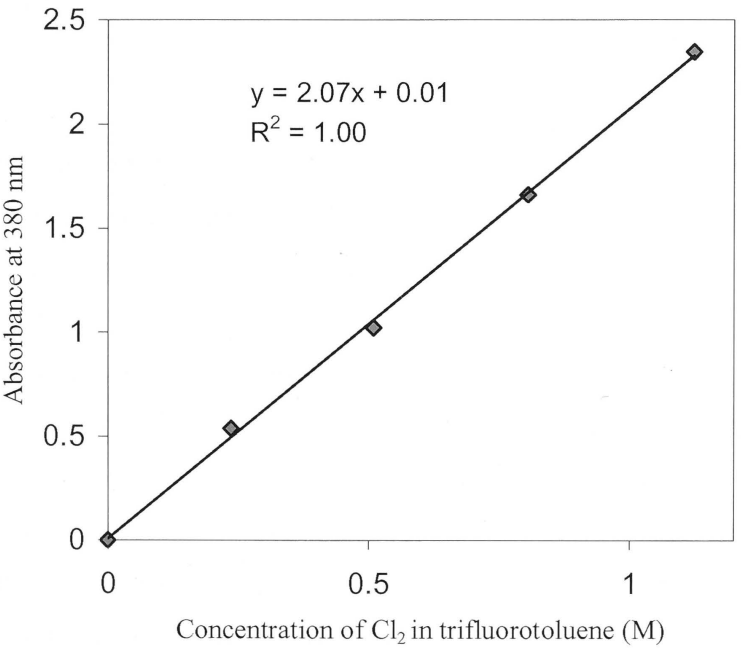
$$Cl_2 + 2KI \rightarrow 2KCl + I_2$$

$$I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$$

The results of these determinations are presented in Table 2.1 and Graph 2.1. The coefficient of absorption for chlorine in trifluorotoluene (Graph 2.1) is about equal to the value obtained with carbon tetrachloride[23] (2.07 compared to 2.16) and both values are higher than that obtained for acetic acid (1.28).[23] This is most likely due to the complex formation between the acetic acid and chlorine as discussed in the Introduction.

Table 2.1 Absorbance of chlorine in trifluorotoluene at 380 nm (path length = 1mm)

Concentration of Cl_2 (M)	Absorbance at 380 nm
0	0
0.237	0.537
0.510	1.024
0.805	1.661
1.123	2.346



Graph 2.1 Absorbance of chlorine in trifluorotoluene at 380 nm (pathlength = 1mm)

2.1 Aromatic Chlorination of Amides

2.1.1 t-Butylbenzene (16)

t-Butylbenzene **(16)** was chosen as an initial substrate for chlorination, because of its simple structure, because it is readily available and moreover it is known that alkylbenzene derivatives chlorinate slowly in carbon tetrachloride, for example both toluene and ethylbenzene show only slow rates of chlorination.[23] Therefore *t*-butylbenzene **(16)** was expected to exhibit a slow rate of chlorination; hence a baseline for comparison with other compounds could be established.

16 **59** **60**

Reaction of *t*-butylbenzene **(16)** with chlorine in trifluorotoluene gave a mixture of the *ortho* and *para* chlorinated products **(59)** and **(60)**. The ^{1}H NMR spectrum of this product mixture (Figure 2.2) shows three distinct methyl resonances at 1.40, 1.22 and 1.17 ppm, which correspond with those of authentic samples of 2-chloro-*t*-butylbenzene **(59)**, starting material **(16)** and 4-chloro-*t*-butylbenzene **(60)** respectively. The aromatic resonances for the starting material **(16)** and the chlorinated isomers **(59)** and **(60)** could not be used for comparative purposes because they fall near the solvent signals, and that region of the spectrum was electronically suppressed.[148] The ratio of *ortho*:*para* substitution for *t*-butylbenzene **(16)** was determined by integration of the ^{1}H NMR spectrum of the product mixture. This ratio was found to be 17:83; the low proportion of the *ortho* isomer obtained is consistent with literature sources[18,20] and can be attributed to steric factors caused by the bulky *t*-butyl group hindering access of the electrophile to the *ortho* position.

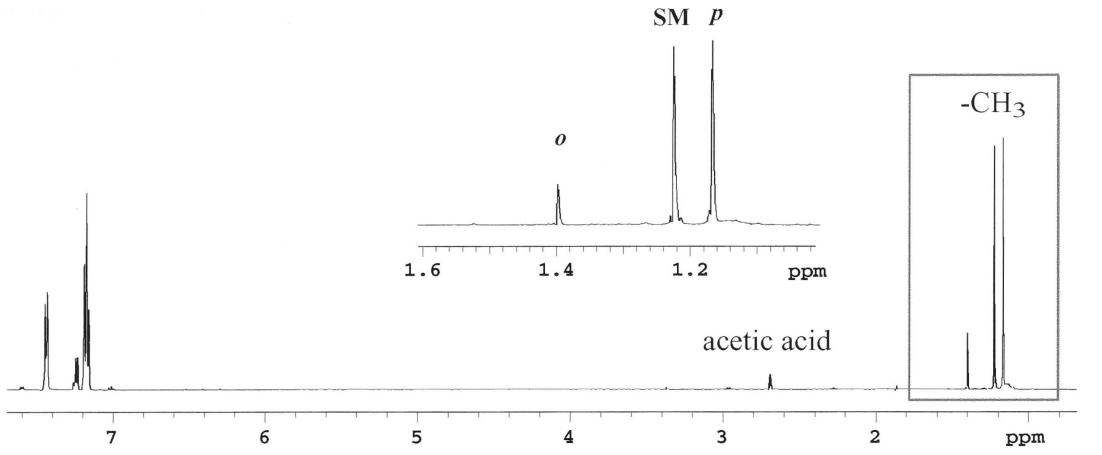
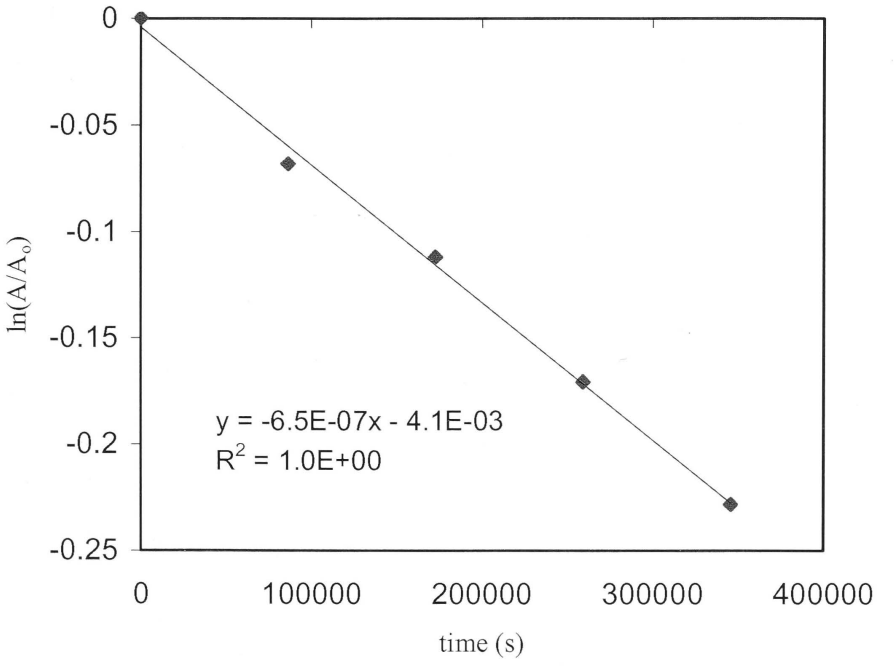


Figure 2.2 ^{1}H NMR spectrum of the product mixture from chlorination of *t*-butylbenzene **(16)** in trifluorotoluene. The methyl signals for the starting material **(16)**, the *ortho* isomer **(59)** and the *para* isomer **(60)** are labelled SM, *o* and *p* respectively.

The methyl resonances for all three components **(16)**, **(59)** and **(60)** were integrated and the percentage of *t*-butylbenzene **(16)** remaining unreacted was calculated by dividing the integral for the *t*-butylbenzene **(16)** resonance by the sum of all three integrals. These data are presented in Table 2.2. A pseudo-first order rate constant of 6.47 x 10^{-7} s^{-1} was obtained from the slope of $\ln([A]/[A]_0)$ plotted against time (Graph 2.2). The concentration used for this reaction was 0.50 M, so a second order rate constant of 1.29 x 10^{-6} $M^{-1}s^{-1}$ was obtained by dividing the pseudo-first order rate constant by the concentration of chlorine in trifluorotoluene. The rate obtained is very slow but not unexpected for the chlorination of *t*-butylbenzene **(16)**. The rate of chlorination of *t*-butylbenzene **(16)** has not been reported in the literature, however, rates of chlorination for related substrates such as toluene and ethylbenzene have been reported in carbon tetrachloride and acetic acid. The second order rate constants for the chlorination of toluene and ethylbenzene in carbon tetrachloride are both 2.8 x 10^{-7} M^{-1} s^{-1},[23] and in acetic acid the rates are 2.7 x 10^{-4} M^{-1} s^{-1},[23] and 2.2 x 10^{-4} M^{-1} s^{-1},[23] respectively. It can be concluded that the chlorination of *t*-butylbenzene **(16)** is slightly faster in trifluorotoluene compared to the rates of reaction of similar substrates such as toluene or ethylbenzene in carbon tetrachloride, but significantly slower then the chlorination of alkylbenzenes in acetic acid.

Table 2.2 Data for the reaction of *t*-butylbenzene **(1)** and chlorine (0.50 M) in trifluorotoluene at 25 °C.

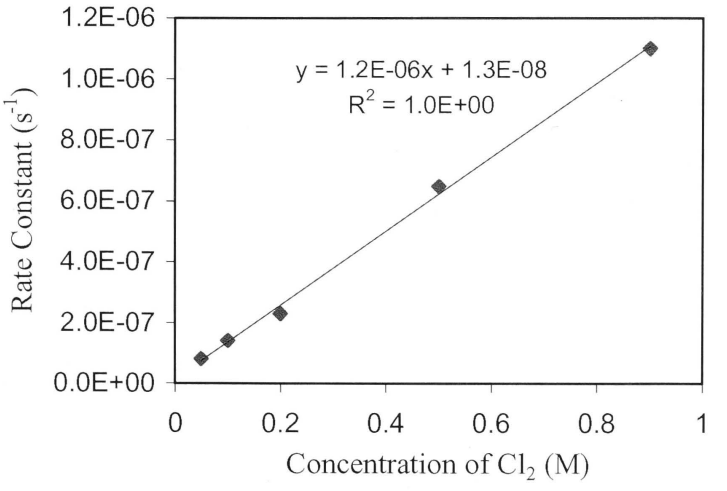
time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_0$	$\ln[A]/[A]_0$
0	100.0	0.0	0.0	1	0
86400	93.5	1.0	5.5	0.934	-0.06828
172800	89.0	2.0	9.0	0.894	-0.11205
259200	84.0	3.0	13.0	0.843	-0.17079
345600	79.5	3.5	17.0	0.796	-0.22816



Graph 2.2 Apparent first order plot for the reaction of *t*-butylbenzene **(16)** with chlorine (0.50 M) in trifluorotoluene at 25 °C.

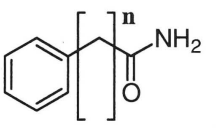
The faster rates of chlorination observed in acetic acid have been discussed in the Introduction, whereby the acetic acid polarises the chlorine making it more electrophilic. The much slower rate of aromatic chlorination in trifluorotoluene can be attributed to a lack of stabilisation of the benzonium ion intermediate by solvation and the weaker electrophilic chlorinating species in trifluorotoluene.

To gather relevant data about the chlorination of *t*-butylbenzene **(16)**, the aromatic **(16)** was treated with chlorine in trifluorotoluene with a range of different chlorine concentrations varying from 0.005 M to 0.90 M (with the relevant data shown in Appendix 1). For experiments performed with low chlorine concentrations (0.005-0.01 M) almost no aromatic chlorination was evident even after 10 days. The values for pseudo-first order rate constants obtained at other concentrations of chlorine show a linear relationship with respect to chlorine concentration. This is typical behaviour of a system following second order kinetics and makes sense for the substrate being studied; an alkylbenzene. The second order rate constant 1.22 x 10^{-6} M^{-1} s^{-1} obtained in this instance from the slope of the plot of pseudo-first order rate constants against chlorine concentration (Graph 2.3) is in good agreement with the value previously obtained (1.28 x 10^{-6} $M^{-1}s^{-1}$) by taking the pseudo-first order rate constant and dividing at 0.50 M chlorine concentration.

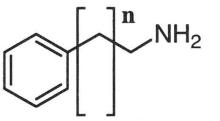


Graph 2.3 Plot of pseudo-first order rate constants for reaction of *t*-butylbenzene **(16)** against chlorine concentration in trifluorotoluene at 25 °C.

The next part of the project involved taking a series of aromatic compounds functionalised with amide and amine moieties (Fig 2.3) that were known to chlorinate much faster than alkylbenzenes in carbon tetrachloride (as discussed in the Introduction) and to study the chlorination of these types of compounds in trifluorotoluene. This was done in order to compare the rates and regioselectivity of aromatic chlorination and ultimately assess whether trifluorotoluene is a suitable replacement solvent for such chemical transformations.



n = 1 phenylacetamide **(31)**
= 2 phenylpropionamide **(32)**
= 3 phenylbutyramide **(33)**

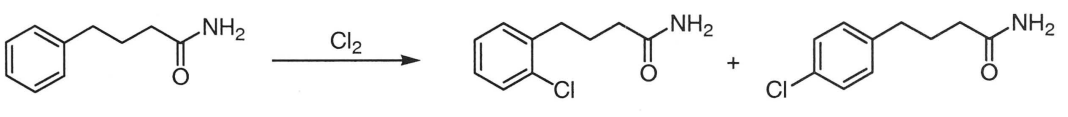


n = 1 phenylethylamine **(40)**
= 2 phenylpropylamine **(41)**
= 3 phenylbutylamine **(42)**

Figure 2.3 The amides and amines chosen for the study of chlorination in trifluorotoluene.

2.1.2 Phenylbutyramide **(33)**

Reaction of phenylbutyramide **(33)** with chlorine in trifluorotoluene produced a clean mixture of the *ortho* and *para* chlorinated products **(61)** and **(62)** in quantitative yield. The products **(61)** and **(62)** were identified by comparisons of ^{1}H NMR spectra and melting points with literature sources.[23,153]



33 **61** **62**

The ^{1}H NMR spectrum of the product mixture (Figure 2.4) contains four methylene resonances with the γ-resonance being distinguishable for the *ortho* and *para* isomers. The amide hydrogen is also seen at about 5.35 ppm and the aromatic resonances overlap.

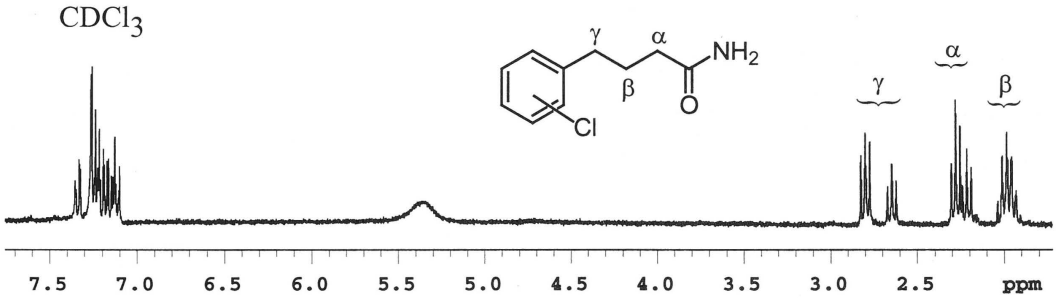


Figure 2.4 ^{1}H NMR spectrum run in $CDCl_3$ of the product mixture from the chlorination of 4-phenylbutyramide **(33)** in trifluorotoluene. The alkyl resonances for the starting material **(33)** and reaction products **(61)** and **(62)** are labelled α-, β- and γ-.

To examine the reaction kinetics, reactions were quenched at specific time intervals of 900, 1800, 3600 and 7200 seconds. Then ^{1}H NMR spectra were run; a typical set of spectra is shown in Figure 2.5. The spectra show methylene peaks for the starting material **(33)** and for each of the *ortho* and *para* chlorinated isomers **(61)** and **(62)**. These spectra are consistent with previous work performed in carbon tetrachloride[23] where similar results were reported after chlorine was removed from the solution. With chlorine present in the reaction mixture, additional resonances were observed and it was suggested that the origins of such peaks were derivatives of the amides **(33)**, **(61)** and **(62)**. Possible explanations for this have been explored and will be discussed later in this chapter.

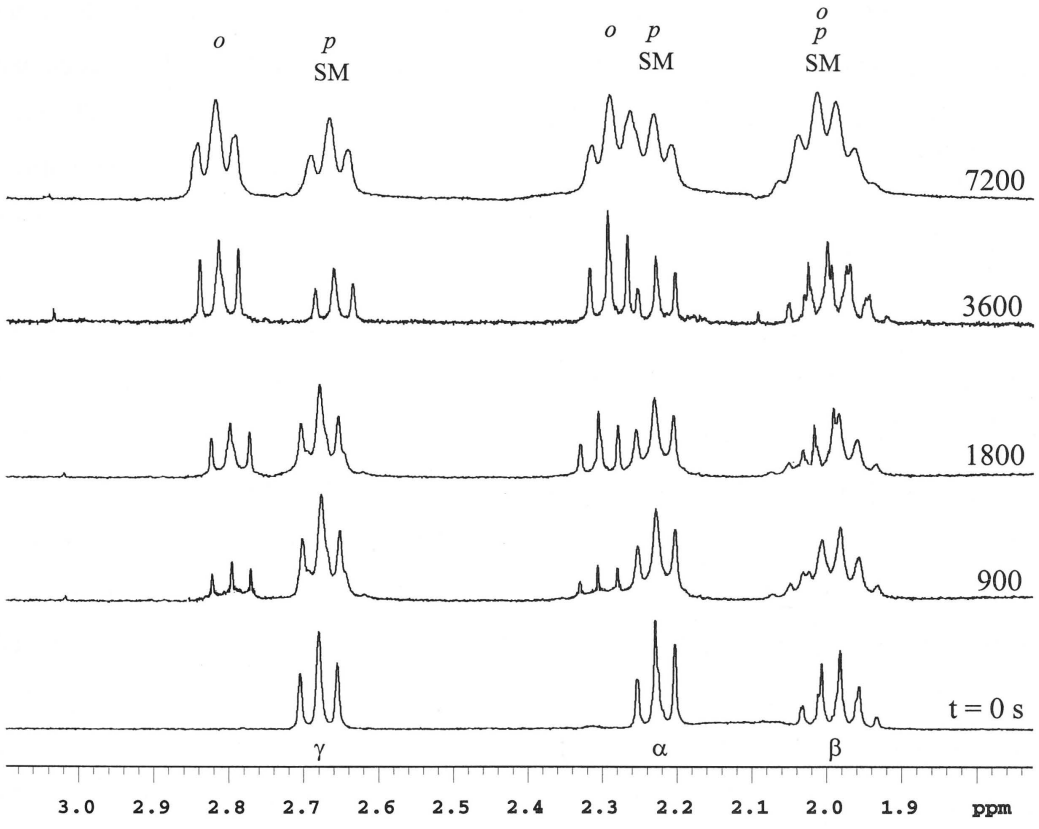


Figure 2.5 Typical set of ^{1}H NMR spectra for the reaction of phenylbutyramide **(33)** with chlorine (0.05 M) in trifluorotoluene. The resonances for the starting material **(33)** and the *ortho* and *para* products **(61)** and **(62)** have been labelled sm, *o* and *p* respectively.

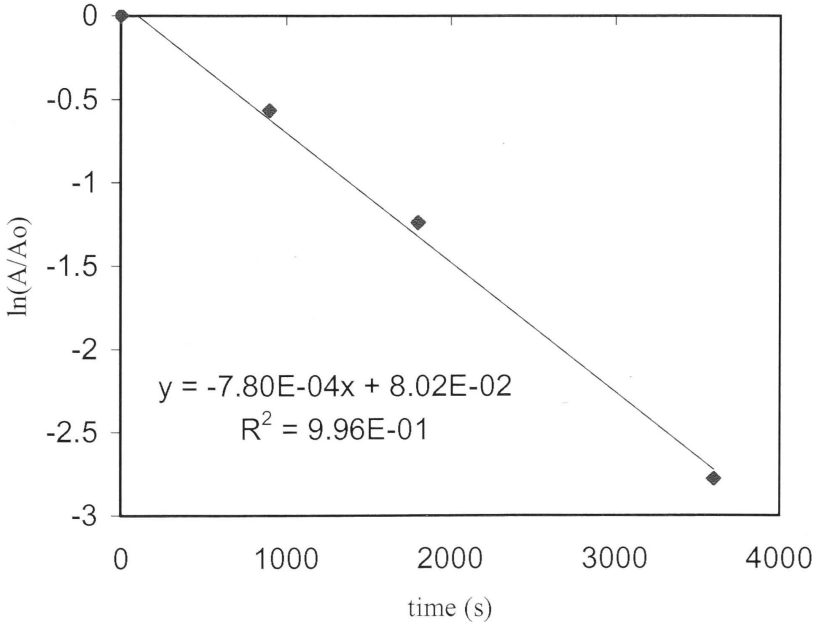
The α-, β- and γ-resonances were assigned on the basis that the deshielding effect of the chlorine on the γ-methylene protons is greater for the *ortho* chlorinated product **(61)** than for the *para* chlorinated product **(62)** and the effect is less significant for α- and β-methylene resonances. This is consistent with the greater shielding effect of the methylene protons from the chlorine in the *ortho* position than the *para* position. The γ-methylene resonance for the *ortho* isomer **(61)** at 2.80 ppm is distinct from the resonances of the starting material **(33)** and *para* isomer **(62)**, which are overlapping at 2.64-2.66 ppm. The overlapping resonances at 2.24-2.28 and 1.99 have been assigned as

due to the α- and β-methylene protons respectively. Integration of the γ-methylene resonances in the ^{1}H NMR spectrum of the product mixture gave an *ortho*/*para* ratio of 55/45. The amount of *ortho* product is slightly higher in this instance than for the chlorination of this amide in carbon tetrachloride where the *ortho* / *para* ratio was 45/55.[23]

The rate of aromatic chlorination was determined by integration of the γ-methylene resonances for the starting material **(33)** and the products **(61)** and **(62)**. The rate of disappearance of the starting material **(33)** was determined by measuring the rate of appearance of the *ortho* isomer **(61)** from the resonance at 2.80 ppm and calculating the fraction of the *para* isomer **(62)** formed from the final *ortho* / *para* product ratio. The slope of Graph 2.4 gives a pseudo-first order rate constant of 7.80×10^{-4} s^{-1} with a relatively dilute solution of chlorine (0.05 M). As will become obvious from further discussion in this chapter, this is not a second order reaction. For a comparison, the pseudo-first order rate constant for the chlorination of *t*-butylbenzene **(16)** in trifluorotoluene with a 0.05 M solution of chlorine is 8.0×10^{-8} s^{-1}. Therefore, the rate of chlorination of phenylbutyramide **(33)** in trifluorotoluene is almost 10,000 times faster than the rate of chlorination of *t*-butylbenzene **(16)** under similar reaction conditions. This rapid increase in rate has been observed in other non-polarising solvents such as carbon tetrachloride,[23] however, the reaction performed in trifluorotoluene was consistently faster than corresponding reaction in carbon tetrachloride. For a comparison between current results and those of experiments performed in carbon tetrachloride, a relevant chlorine concentration that was similar in both cases was chosen. Comparisons of pseudo-first order rate constants were made at a chlorine concentration of around 1.0 M. The chlorination of the amide **(33)** in trifluorotoluene is more than five times faster than in carbon tetrachloride with respective pseudo-first order rate constants being 2.6×10^{-3} s^{-1} at a chlorine concentration of 1.01 M compared to 4.4×10^{-4} s^{-1} at a chlorine concentration of 1.29 M. The relatively fast rate of aromatic chlorination is related to the formation of an intermediate as discussed in the Introduction, and below.

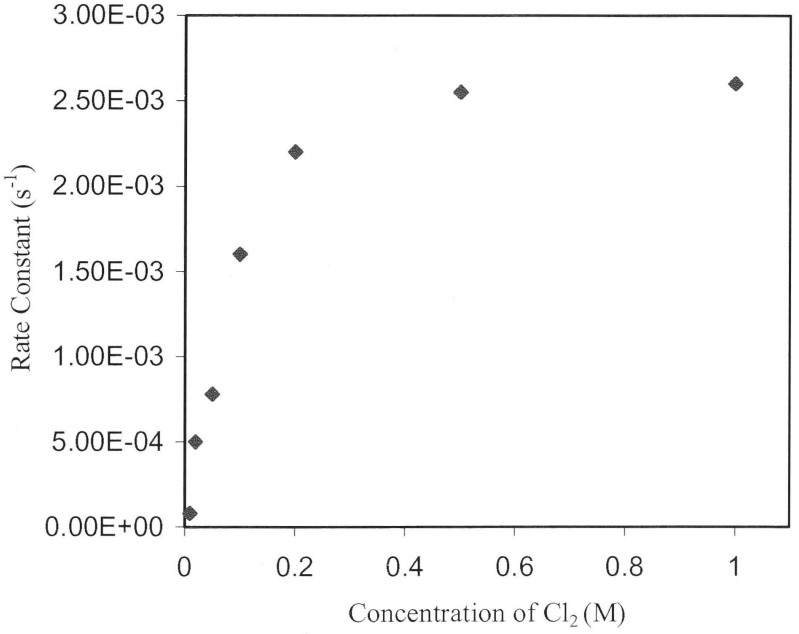
Table 2.3 Data for the reaction of phenylbutyramide **(33)** and chlorine (0.05 M) in trifluorotoluene at 25 °C.

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_0$	$\ln[A]/[A]_0$
0	100.0	0	0	1.000	0
900	56.5	24.0	19.5	0.566	-0.569
1800	29.0	39.0	32.0	0.289	-1.241
3600	6.5	51.5	42.0	0.062	-2.780
7200	0.0	55.0	45.0	0.000	N/A



Graph 2.4 Apparent first order plot for the reaction of phenylbutyramide **(33)** with chlorine (0.05 M) in trifluorotoluene at 25 °C.

Phenylbutyramide **(33)** was subsequently chlorinated in trifluorotoluene with different concentrations of chlorine to obtain rate constants at different chlorine concentrations and to establish if there is a relationship between the pseudo-first order rate constant and chlorine concentration (the relevant data for each point on the graph is presented in Appendix 1). The plot for pseudo-first order rate constants against chlorine concentration is presented in Graph 2.5.

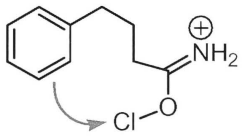


Graph 2.5 Apparent pseudo-first order rate constants for the aromatic chlorination of phenylbutyramide **(33)** in trifluorotoluene at 25 °C as a function of the concentration of chlorine.

The results presented in Graph 2.5 indicate that there is a relationship between the rate constants and the concentration of chlorine, but this is clearly not a linear type of dependence as was observed for *t*-butylbenzene **(16)**. From the shape of the curve it can be concluded that the rate is slow for very dilute solutions of chlorine, and increases substantially until it flattens out. The maximum pseudo-first order rate constant achieved

is 2.60 x 10^{-3} s^{-1}. The fact that the curve flattens out is indicative of a limiting factor and suggests that there is the formation of an intermediate species or at least some source of intra-molecular activated chlorine species. Therefore it can be concluded that this is not a second order process, and the conversion of these values obtained for pseudo-first order rate constants into second order rate constants makes no sense. The only way of comparing relative rates of chlorination is to compare pseudo-first order rate constants at the same or similar chlorine concentrations.

The rapid increase in rate of aromatic chlorination of phenylbutyramide **(33)** in carbon tetrachloride was attributed to the formation of the *O*-chloro imidate species **(23)**.[23] It is believed that the same species is formed in trifluorotoluene and is responsible for the rapid increase in rate of aromatic chlorination. Two reasons for such a claim are; firstly, there is formation of a more electrophilic source of chlorine than molecular chlorine, by polarisation of the chlorine bond, and secondly, the close proximity of the chlorinating species to the ring, allows intramolecular chlorination.



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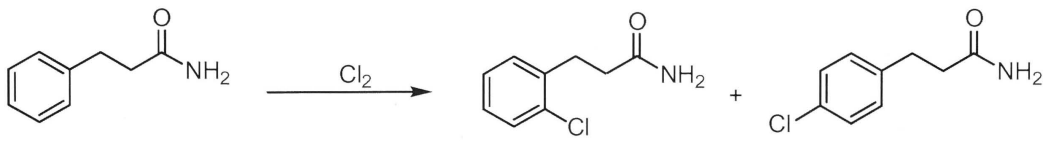
2.1.3 Phenylpropionamide **(32)**

Reaction of phenylpropionamide **(32)** with chlorine in trifluorotoluene gave a mixture of the *ortho* and *para* chlorinated products **(63)** and **(64)** in quantitative yield.



(32) **(63)** **(64)**

The products **(63)** and **(64)** were identified by comparison of their ^{1}H NMR spectra and melting points with literature data.[154,155] An *ortho* / *para* ratio of 55 / 45 was obtained by integration of the β-methylene resonances in the ^{1}H NMR spectrum of the reaction mixture. The *ortho* / *para* ratio obtained in this instance is the same as that for the chlorination of the substrate in carbon tetrachloride.

To examine the reaction kinetics, reactions were quenched at specific time intervals of 900, 1800, 3600 and 7200 seconds. Then ^{1}H NMR spectra were run; a typical set of spectra is shown in Figure 2.6. The spectra shown in Figure 2.6 show methylene peaks for the starting material **(32)** and for each of the *ortho* and *para* chlorinated isomers **(63)** and **(64)**.

The α- and β-resonances were assigned on the same basis as that used to assign the spectra of products for the analogous chlorination of phenylbutyramide **(32)**. The β-methylene resonance for the *ortho* isomer **(63)** at 3.10 ppm is distinct from the resonances of the starting material and *para* isomer, which are overlapping at 2.96-2.98 ppm. The overlapping resonances at 2.54-2.57 ppm have been assigned as the α-methylene resonances for the starting material **(32)** and the *ortho* and *para* chlorinated products **(63)** and **(64)**.

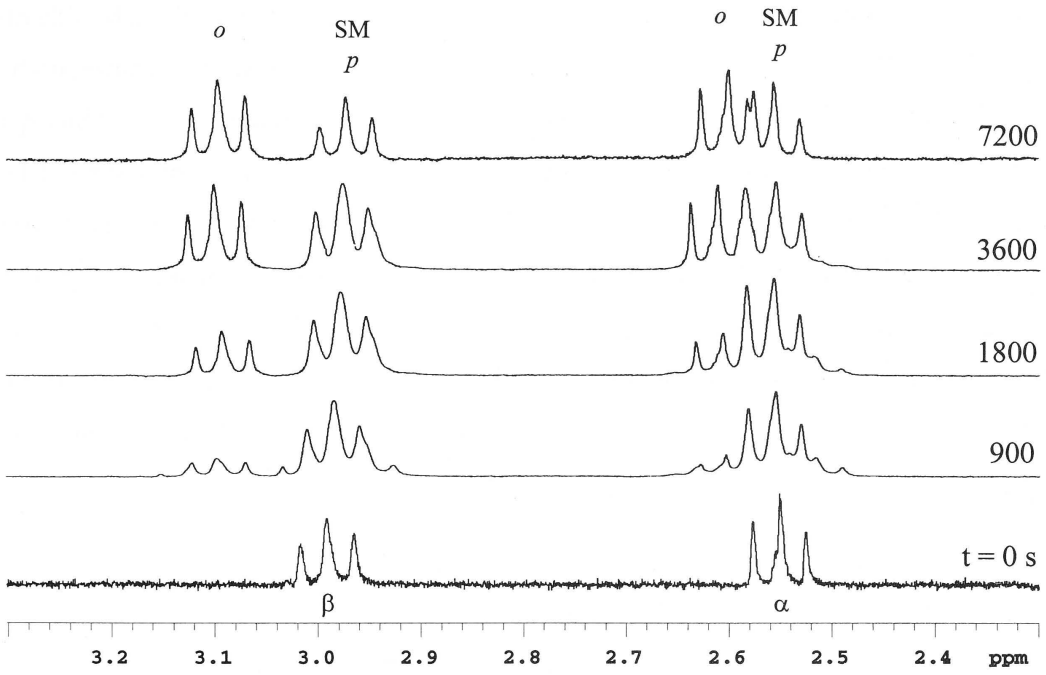
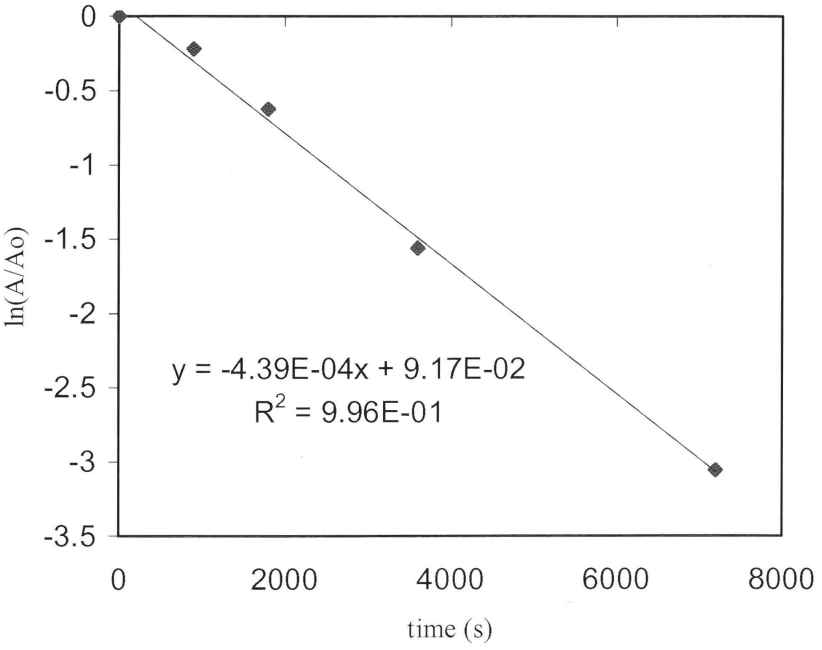


Figure 2.6 Typical set of ^{1}H NMR spectra for the reaction of phenylpropionamide **(32)** with chlorine (0.05 M) in trifluorotoluene. The resonances for the starting material **(32)** and the *ortho* and *para* chlorinated products **(63)** and **(64)** have been labelled sm, *o* and *p* respectively.

The rate of aromatic chlorination was determined by integration of the β-methylene resonances for the starting material **(32)** and the products **(63)** and **(64)**. So the rate of disappearance of the starting material **(32)** was determined by measuring the rate of appearance of the *ortho* isomer **(63)** from the resonance at 3.10 ppm and calculating the fraction of the *para* isomer **(64)** formed from the final *ortho* / *para* product ratio. The slope of Graph 2.6 gives a pseudo-first order rate constant of 4.39×10^{-4} s^{-1} with a relatively dilute solution of chlorine (0.05 M). For a comparison, the pseudo-first order rate constant for the chlorination of *t*-butylbenzene **(16)** in trifluorotoluene with a 0.05 M solution of chlorine is 8.0×10^{-8} s^{-1}. Therefore, the rate of chlorination of phenylpropionamide **(32)** in trifluorotoluene is almost 5,500 times faster than the rate of chlorination of *t*-butylbenzene **(16)** under similar reaction conditions. This increase in rate has been observed for chlorinations of phenylpropionamide **(32)** in carbon

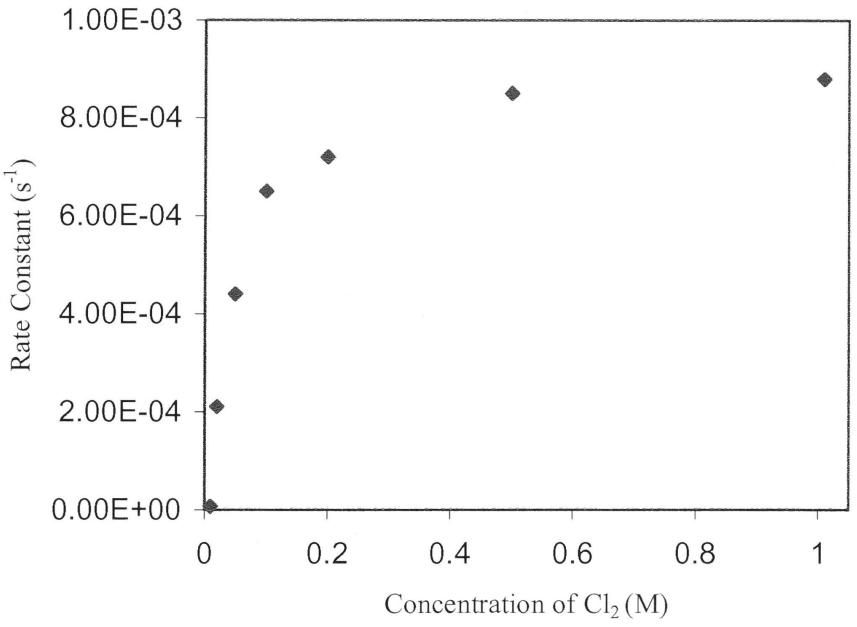
tetrachloride,[23] however, reactions performed in trifluorotoluene are faster than those in carbon tetrachloride as was the case with the previously studied amide **(33)**. Comparisons of pseudo-first order rate constants were made at chlorine concentrations near 0.10 M, and the reaction in trifluorotoluene is almost four times faster than the corresponding reaction in carbon tetrachloride. The pseudo-first order rate constants in trifluorotoluene and carbon tetrachloride (with chlorine concentrations shown in brackets) are 1.7×10^{-4} s^{-1} (0.127 M) and 6.5×10^{-4} s^{-1} (0.10 M) respectively. It seems likely that the relatively fast rate of aromatic chlorination is related to the formation of an intermediate, as was the case with the longer chained amide **(33)**.



Graph 2.6 Apparent first order plot for the reaction of phenylpropionamide **(32)** with chlorine (0.05 M) in trifluorotoluene at 25 °C. The data for this graph are presented in Appendix 1.

Phenylpropionamide **(32)** was subsequently chlorinated in trifluorotoluene with different concentrations of chlorine to obtain rate constants at different chlorine concentrations (with the relevant data presented in Appendix 1) and to see if there was a relationship between the pseudo-first order rate constant and chlorine concentration such as that found

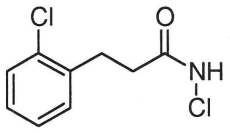
for phenylbutyramide **(33)**. The plot for pseudo-first order rate constants against chlorine concentration is presented in Graph 2.7.



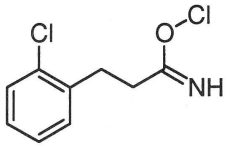
Graph 2.7 Apparent pseudo-first order rate constants for the aromatic chlorination of phenylpropionamide **(32)** in trifluorotoluene at 25 °C as a function of the concentration of chlorine.

The results presented in Graph 2.7 are very similar to those obtained for phenylbutyramide **(33)** and indicate that there is a relationship between the rate constants and the concentration of chlorine, and just as was the case for phenylbutyramide **(33)**, it is obvious from the plot that there is no linear dependence. The maximum pseudo-first order rate constant achieved for the aromatic chlorination of phenylpropionamide **(32)** is 8.80×10^{-4} s^{-1}. As was the case with phenylbutyramide **(33)** the graph has the same characteristic shape whereby the curve flattens out and therefore is indicative of a limiting factor, hence it can be concluded that this is not a second order process. It is believed that there is the formation of an intermediate species (similar to that responsible for rapid chlorination of phenylbutyramide **(33)**).

For work performed on the chlorination of phenylpropionamide **(32)** in carbon tetrachloride,[23] it was found that as soon as chlorine was added to a solution of amide, additional resonances were observed in the ^{1}H NMR spectrum and it was suggested that there was formation of some sort of derivative species, which subsequently was found to be the *N*-chloroamide species. To further test the hypothesis that an activated chlorinating species was forming in this particular case; a monochlorinated isomer of phenylpropionamide, in this case the *ortho* isomer **(63)**, was subjected to solutions of trifluorotoluene with different chlorine concentrations. It was considered that with such a compound **(63)**, further chlorination on the aromatic ring would be unlikely because the ring would be sufficiently deactivated. So the only possible formation of products would be the *N*-chloroamide **(65)** or the analogous *O*-chloroimidate **(66)** and their corresponding salts.



65



66

Observations of an intermediate were made using ^{1}H NMR spectroscopy under solvent suppression conditions.[148] Formation of a new set of resonances was observed in the spectrum (Figure 2.7) and it was apparent that the new peak forming at 3.14 ppm was most likely due to the formation of a derivative species. Both peak height comparisons and integration were used to quantify the yield of the intermediate product, which is best seen in Figure 2.7.

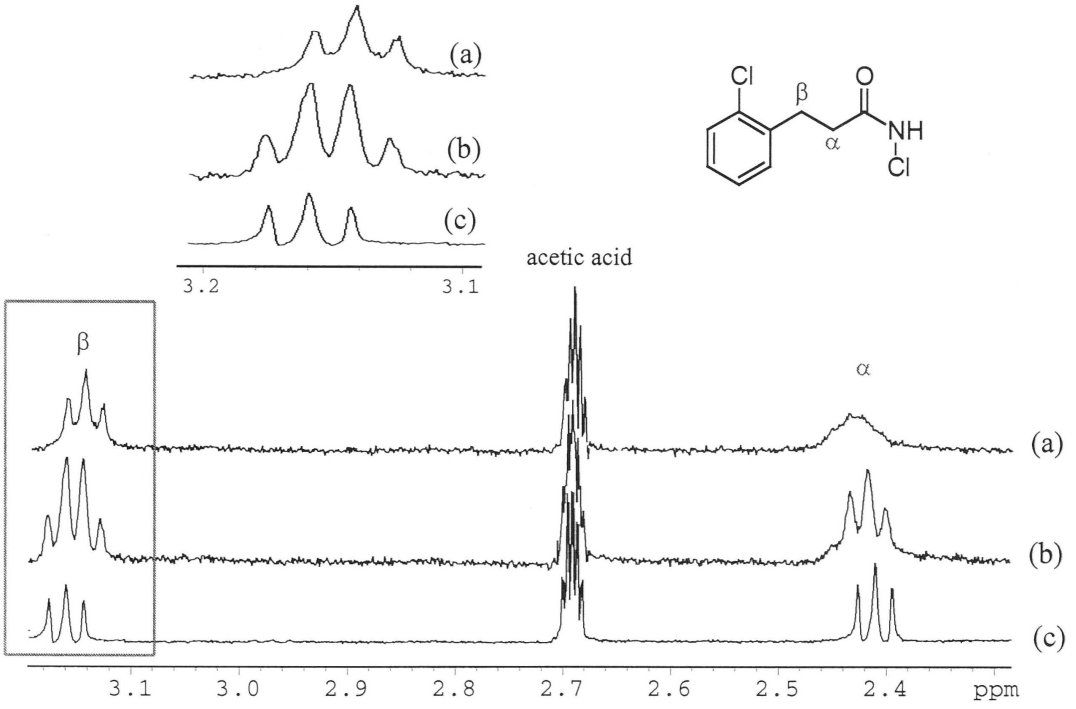
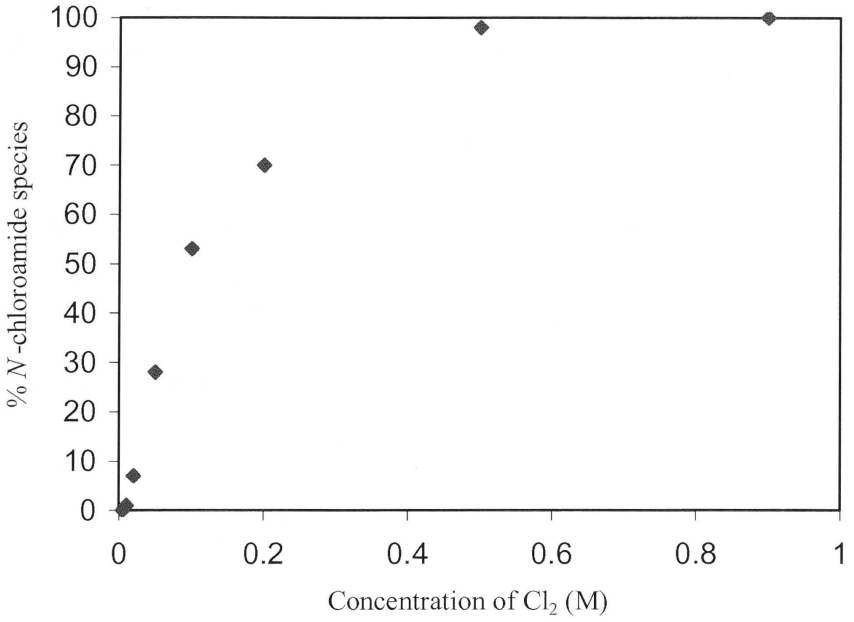


Figure 2.7 ^{1}H NMR spectra of the β-methylene resonances of the *ortho* chlorinated amide **(63)** in trifluorotoluene at 25 °C, with (a) no chlorine, (b) 0.10 M chlorine and (c) 0.90 M chlorine.

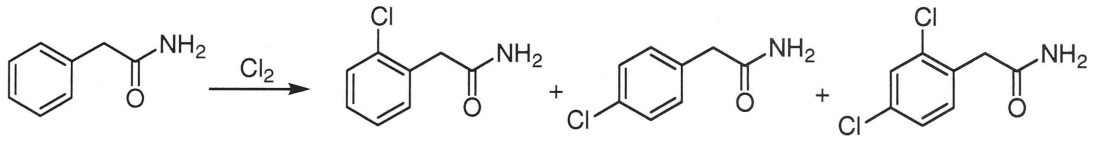
From the results presented in Graph 2.8 it can clearly be seen that the curve obtained is a notable resemblance of that obtained for Graph 2.7. It indicates that there is formation of an intermediate and more importantly the rate of reaction parallels the formation of this species at equilibrium. As discussed in the introduction, the intermediate observed in the ^{1}H NMR spectrum is the *N*-chloroamide, however it has been ruled out as intermediate responsible for the rapid increase in rate of aromatic chlorination. Previous studies in carbon tetrachloride[23] concluded that it was the *O*-chloroimidate species that was responsible for the rapid increase in rate of aromatic chlorination and exactly the same intermediate is believed to be imparting this significant affect in this case.



Graph 2.8 Percentage of the *N*-chloroamide **(65)** formed from *o*-chloro-3-phenylpropionamide **(63)** as a function of chlorine concentration in trifluorotoluene at 25 °C.

2.1.4 Phenylacetamide **(31)**

To determine if the intramolecular aromatic chlorination of phenylbutyramide **(33)** and phenylpropionamide **(32)** was a general effect observed for other phenylalkylamides and the effect, if any, of a shorter alkyl chain, phenylacetamide **(31)** was reacted with chlorine in trifluorotoluene. The product of this reaction was a mixture of predominantly the *ortho* chlorinated isomer **(67)** and the *para* chlorinated isomer **(68)**. A minute amount of the 2,4-dichlorinated product **(69)** was observed towards the later stages of reaction when using chlorine concentrations ≥0.5 M. The products **(67)**, **(68)** and **(69)** were identified by comparison of their ^{1}H NMR spectra and/or melting points with literature data.[156,157]



31 **67** **68** **69**

Reaction kinetics were examined in a similar manner to that discussed earlier for the previous two amides **(33)** and **(32)**, whereby reactions were quenched at specific time intervals. However, significantly longer reaction times were needed to observe appreciable levels of consumption of starting material. A typical set of spectra is shown in Figure 2.8.

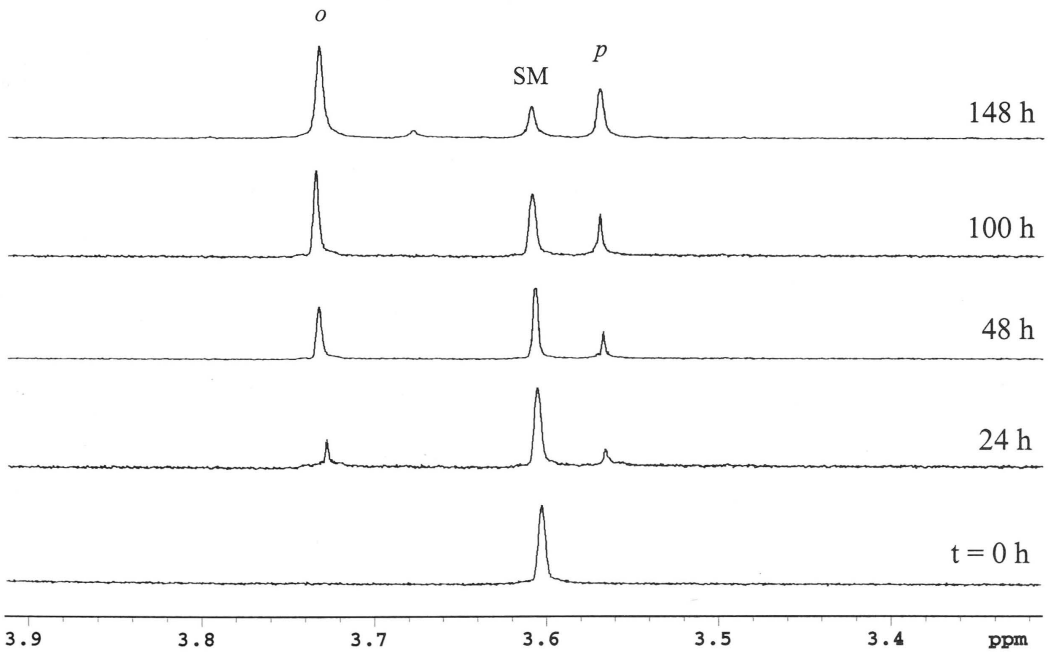
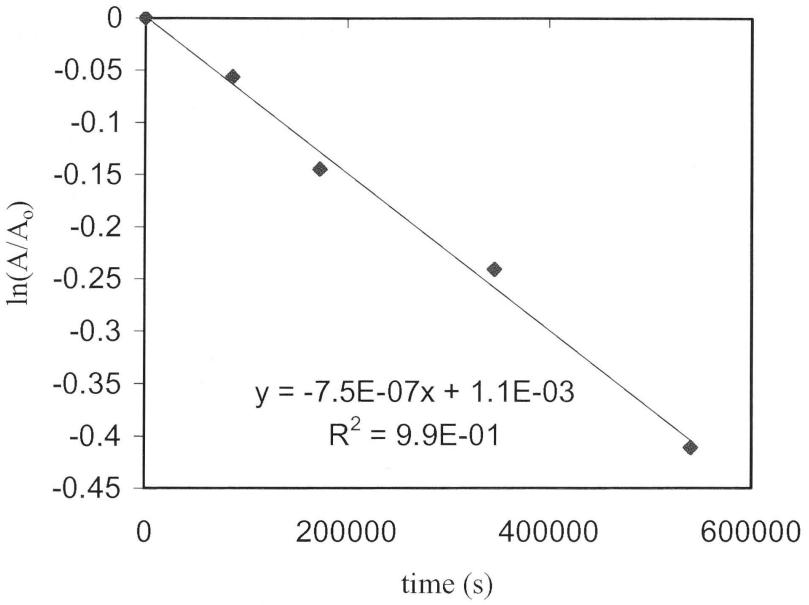


Figure 2.8 Typical set of ^{1}H NMR spectra for the reaction of phenyacetamide **(31)** with chlorine (0.20 M) in trifluorotoluene. The resonances for the starting material **(31)** and the *ortho* and *para* chlorinated products **(67)** and **(68)** have been labelled sm, *o* and *p* respectively. A new resonance observed at 3.69 ppm, after 148 hours of reaction suggests the formation of the 2,4-dichlorinated product **(69)**.

The resonances were assigned on the same basis as that used to assign the spectra of products for the analogous chlorination of the previous two amides **(33)** and **(32)**, where it was noted that the deshielding effect of the chlorine on the methylene protons is greater for the *ortho* product **(67)** than the *para* **(68)**. The methylene chemical shifts for the *ortho* and *para* chlorinated isomers **(67)** and **(68)** were 3.73 and 3.56 ppm respectively, quite distinct form that of starting material **(31)** at 3.60 ppm. An *ortho* / *para* ratio of 64 / 36 was obtained by integration of the methylene resonances in the ^{1}H NMR spectrum of the reaction mixture. The *ortho* / *para* ratio obtained here is almost identical to the value 63 / 37 obtained for the chlorination of the same substrate in carbon tetrachloride,[23] however no formation of the 2,4-dichloro compound **(69)** was noted in that particular study.

The rate of aromatic chlorination was determined by integration of the methylene resonances for the starting material **(31)** and the products **(67)**, **(68)** and **(69)**. It is important to note that the dichlorinated product **(69)** was observed in very small quantities towards the latter stages of reaction. As such it is not discussed to the same extent as the major products; the *ortho* and *para* isomers **(67)** and **(68)**. The rate of disappearance of the starting material **(31)** was determined by measuring the rate of appearance of the *ortho* and *para* isomers **(67)** and **(68)** from the resonances at 3.73 and 3.56 ppm respectively.

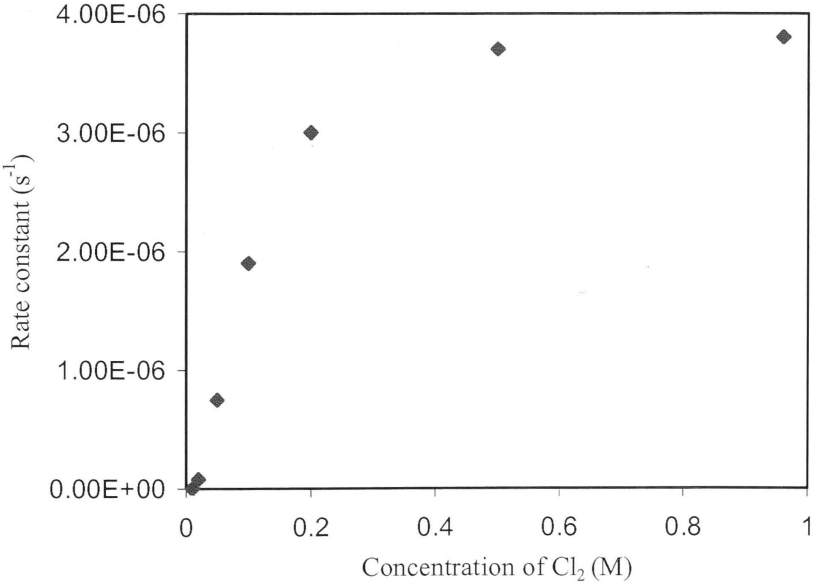


Graph 2.9 Apparent first order plot for the reaction of phenylacetamide **(31)** with chlorine (0.05 M) in trifluorotoluene at 25 °C.

The slope of Graph 2.9 gives a pseudo-first order rate constant of 7.5 x 10^{-7} s^{-1} with a chlorine concentration of (0.05 M). The rate of aromatic chlorination of phenylacetamide **(31)** is considerably slower than the rates of reaction of the previous amides **(33)** and **(32)**. For a comparison, the pseudo-first order rate constant for the chlorination of *t*-butylbenzene **(16)** in trifluorotoluene with a 0.05 M solution of chlorine is 8.0 x 10^{-8} s^{-1}. Therefore, the rate of chlorination of phenylacetamide **(31)** in trifluorotoluene is almost 10 times faster than the rate of chlorination of *t*-butylbenzene **(16)** under similar reaction conditions, although it is more than one hundred times slower than the rates of reaction of the previous amides **(33)** and **(32)**. A similar trend has been noted for the aromatic chlorination of amides in carbon tetrachloride,[23] where the rate of chlorination for phenylacetamide **(31)** is much slower than those of the longer chained amides **(33)** and **(32)**. It should be noted that the rate of aromatic chlorination of phenylacetamide **(31)** is slightly faster in trifluorotoluene than carbon tetrachloride; this comparison was also observed for the amides **(33)** and **(32)** studied above. Aromatic chlorination of the amide **(31)** is almost two times faster in trifluorotoluene compared to carbon tetrachloride. The

fact that the rate of aromatic chlorination of phenylacetamide **(31)** is almost 10 times as fast as the chlorination of *t*-butylbenzene **(16)** suggests that there was formation of an activating intermediate. Subsequently, phenylacetamide **(31)** was reacted in trifluorotoluene with varying concentrations of chlorine to see if there was a relationship between the pseudo-first order rate constant and chlorine concentration.

The results are presented in Graph 2.10 and are very similar to those obtained for the other amides **(33)** and **(32)** and indicate that the rate constant is dependent on the chlorine concentration, however this is not a linear type of dependence. The maximum pseudo-first order rate constant achieved is 3.8×10^{-6} s^{-1}. As was the case with the previously studied amides **(33)** and **(32)**, the graph has the same characteristic shape whereby the curve flattens out and as seen and discussed before is indicative of a limiting factor, hence it can be concluded that this is not a second order process. It was suggested that there is the formation of an intermediate species or at least some source of intra-molecular activated chlorine species.



Graph 2.10 Apparent pseudo-first order rate constants for the aromatic chlorination of phenylacetamide **(31)** in trifluorotoluene at 25 °C as a function of the concentration of chlorine.

The species responsible for the increase in rate of aromatic chlorination is believed to be the *O*-chloroimidate. This is consistent with observations made with the longer chained amides **(33)** and **(32)**. It seems reasonable to assume that the aromatic chlorination of phenylacetamide **(31)** proceeds *via* the formation of an activated intermediate because firstly, the rate is about one order of magnitude faster than the rate of aromatic chlorination of simple alkylbenzenes such as *t*-butylbenzene **(16)**, and secondly, the relationship between pseudo-first order rate constants as a function of chlorine is similar to those seen with the previously studied amides **(33)** and **(32)**. Despite these assumptions, the rate of aromatic chlorination of phenylacetamide **(31)** is many times slower than those of the initial amides **(33)** and **(32)** studied. Several possible explanations were considered for the difference in rate of aromatic chlorination of phenylacetamide **(31)** and the other amides **(33)** and **(32)**. If the mechanism of chlorination of phenylacetamide **(31)** in trifluorotoluene is intramolecular, as suggested for the other amides **(33)** and **(31)**, then it is possible that chlorination is slower because the alkyl chain is too short to bend around and interact with the aromatic ring as efficiently as possible for the longer-chained amides **(33)** and **(32)**. For the same reason the reaction of the acetamide **(31)** may in fact be intermolecular.[23]

Another possibility is that the amide group of phenylacetamide **(31)** is deactivating the aromatic ring and slows the rate of aromatic chlorination. Studies have shown that when phenylacetamide **(31)** and phenylpropionamide **(32)** were chlorinated in acetic acid[23] the second order rate constant for reaction of phenylacetamide **(31)** was more than one order of magnitude less than the rate constant determined for phenylpropionamide **(32)**. This indicated that the aromatic chlorination of phenylacetamide **(31)** is slower because of an inductive effect of the amide group. It was previously mentioned in the Introduction that inductive effects drop off rapidly with increasing distance from the aromatic ring.

The *ortho* / *para* substitution ratio of 64/36 obtained for the aromatic chlorination of phenylacetamide **(31)** in trifluorotoluene is lower than might be expected for an intramolecular reaction. This suggests that the aromatic chlorination of phenylacetamide **(31)** in trifluorotoluene occurs at least partly *via* an intermolecular mechanism which would not be expected to be as regioselective as an intramolecular mechanism.

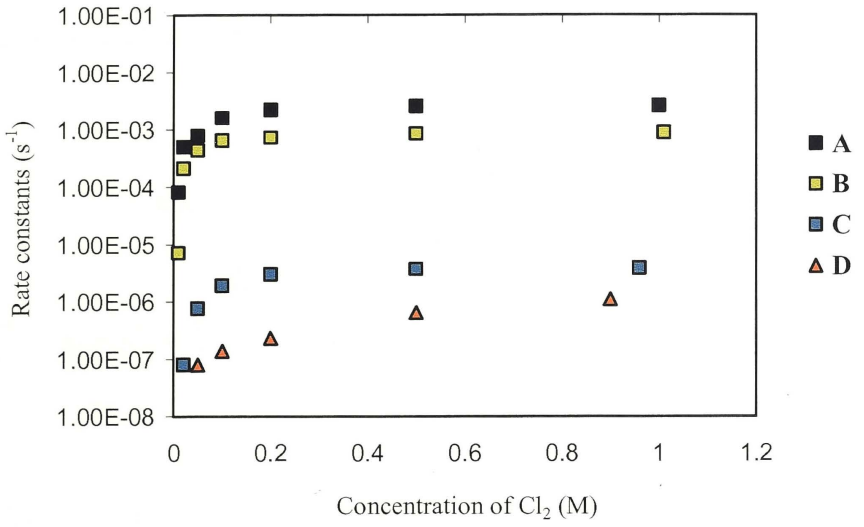
2.2 Summary of rate constants

It can be seen that very fast rates of aromatic chlorination are achieved in trifluorotoluene and the results (summarised in Table 2.4) presented here are very similar to those obtained for previously performed work in carbon tetrachloride. Rate increases of more than three orders of magnitude are observed for the two longer chained amides **(32)** and **(33)** compared to *t*-butylbenzene **(16)** using the current reaction protocol.

Table 2.4 A summary and comparison of pseudo-first order rate constants for the aromatic chlorination of substrates in trifluorotoluene and carbon tetrachloride at 25 °C.

Substrate		Pseudo-first order rate constant in $PhCF_3$	*o* / *p*	$[Cl_2]$/M	Pseudo-first order rate constant in CCl_4	*o* /*p*	$[Cl_2]$/ M
t-butylbenzene	**(16)**	6.5×10^{-7}	17:83	0.50	-	-	-
Phenylbutyramide	**(33)**	2.5×10^{-3}	55:45	0.50	4.4×10^{-4}	45:55	1.29
Phenylpropionamide	**(32)**	8.5×10^{-4}	55:45	0.50	1.7×10^{-4}	55:45	0.127
Phenylacetamide	**(31)**	3.7×10^{-6}	64:36	0.50	2.1×10^{-6}	63:37	0.833

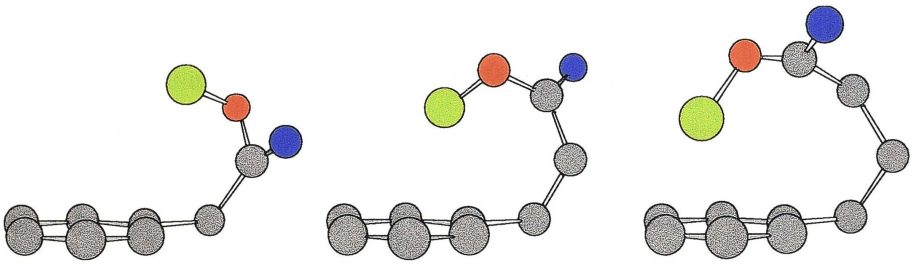
As a general trend, slightly faster rates of aromatic chlorinations in trifluorotoluene are observed for all substrates studied compared to those done in carbon tetrachloride. It can clearly be seen that phenylbutyramide **(33)** has the fastest rate of chlorination, with phenylpropionamide **(32)** being slightly slower, whilst phenylacetamide **(31)** is significantly slower than the two longer chained amides **(33)** and **(32)**. Graph 2.11 shows a relative comparison of the pseudo-first order rate constants for reaction of the amides **(33)**, **(32)** and **(31)** and *t*-butylbenzene **(16)**.



Graph 2.11 A summary of the pseudo-first order rate constants for reaction of (A) phenylbutyramide **(33)**, (B) phenylpropionamide **(32)**, (C) phenylacetamide **(31)** and (D) *t*-butylbenzene **(16)**. It is important to note that the Y-axis for the graph presented has deliberately been given a logarithmic scale to make relative comparisons.

The *ortho* / *para* substitution ratio for the chlorination of the two longer chained amides **(33)** and **(32)** is lower than that observed for phenylacetamide **(31)**. As previously discussed, it was expected for an intramolecular reaction that the length of the alkyl chain would have an effect on the *ortho*/*para* product ratios. A longer chain length would enable greater *para* substitution. Figure 2.9 is an illustration of the accessibility of chlorine to the aromatic ring for the *O*-chloroimidates. From the Chem3D™ structures it can be seen that in the case of the *O*-chloroimidate **(70)**, the chlorine is effectively restricted to interaction with the *ortho* position while the other *O*-chloroimidates **(71)** and **(72)** allow sufficient *ortho* and *para* interaction. It is therefore surprising that aromatic substitution of phenylacetamide **(31)** results in so much *para* product. It seems likely that in this case aromatic chlorination proceeds at least partly via an intermolecular mechanism. The difference in rate of aromatic chlorination between the amides can also be attributed to the length of the alkyl chained, and furthermore, as discussed it is highly

likely that the mechanism for chlorination of phenylacetamide **(31)** is a combination of intramolecular and intermolecular.



70 **71** **72**

Figure 2.9 Chem3D™ representations of the molecular structures of the *O*-chloroimidates **(70)**, **(71)** and **(72)**. Chlorines are represented in green and Hydrogens have been omitted for clarity.

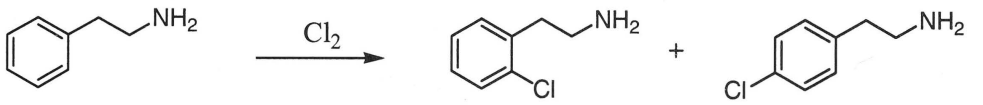
2.3 Aromatic Chlorination of Amines

Rapid rates for aromatic chlorination were observed with amides as previously discussed. It was envisaged that these types of chlorinations could well be extended towards alkylamine analogues of the amides, because previous studies on aromatic chlorination performed in carbon tetrachloride[23] showed that amines might be chlorinated rapidly. It was also suggested that the rapid rate of aromatic chlorination was due to the formation of an intermediate.

Phenylethylamine **(40)**, phenylpropylamine **(41)** and phenylbutylamine **(42)** were treated with a 0.5 M chlorine solution in trifluorotoluene at room temperature in the absence of light for 8 hours. Upon addition of the chlorinated solution there was immediate formation of a white solid. The reactions were quenched in the usual manner by blowing nitrogen over the mixture to leave a white solid. Products of all three amines **(40)**, **(41)** and **(42)** were not soluble in *d*-chloroform, so ^{1}H NMR spectra were run in d_4-acetic acid and the products were characterised as their acetate salts.

2.3.1 Phenylethylamine **(40)**

Reaction of phenylethylamine **(40)** with chlorine in trifluorotoluene gave a mixture of the *ortho* and *para* chlorinated products **(73)** and **(74)** in quantitative yield. The products **(73)** and **(74)** were identified by comparison of their ^{1}H NMR spectra and/or melting points with literature data.[23]



40 **73** **74**

An *ortho* / *para* ratio of 81:19 was obtained by integration of the β-methylene resonances in the ^{1}H NMR spectrum of the reaction mixture (Figure 2.10). The *ortho*/*para* ratio obtained in this instance is lower than that for the chlorination of the substrate in carbon tetrachloride, where only the *ortho* isomer **(73)** was observed.

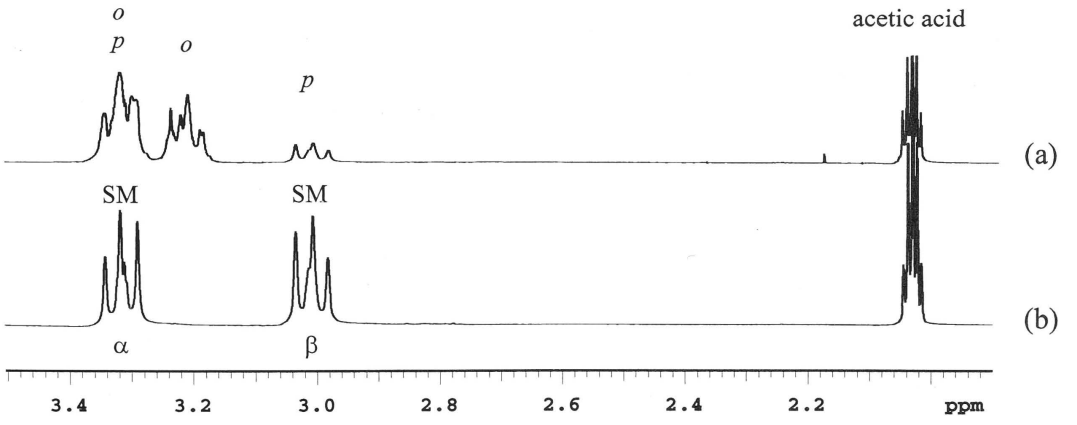
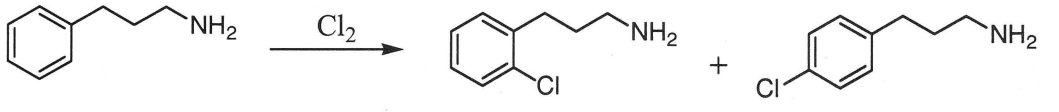


Figure 2.10 ^{1}H NMR spectra in acetic acid-d_4 of (a) the product mixture from chlorination of phenylethylamine **(40)** in trifluorotoluene and (b) starting material **(40)**. The resonances for the starting material and the *ortho* and *para* substitution products **(73)** and **(74)** have been labelled sm, *o* and *p* respectively.

2.3.2 Phenylpropylamine **(41)**

Reaction of phenylpropylamine **(41)** with chlorine in trifluorotoluene gave a mixture of the *ortho* and *para* chlorinated products **(75)** and **(76)** in quantitative yield. The products **(75)** and **(76)** were identified by comparison of their ^{1}H NMR spectra and/or melting points with literature data.[23]



41 **75** **76**

An *ortho*/*para* ratio of 67:33 was obtained by integration of the γ-methylene resonances in the ^{1}H NMR spectrum of the reaction mixture (Figure 2.11). The *ortho*/*para* ratio obtained in this instance is lower than that for the chlorination of the substrate in carbon tetrachloride, where the value was 77:23 *ortho*/*para*.

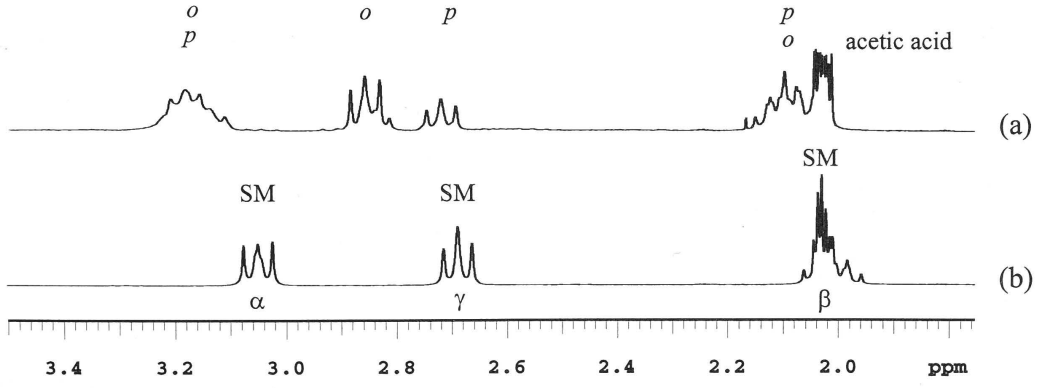
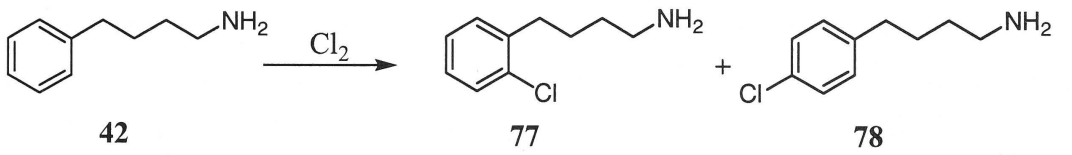


Figure 2.11 ^{1}H NMR spectra in acetic acid-d_4 of (a) the product mixture from chlorination of phenylpropylamine **(41)** in trifluorotoluene and (b) starting material **(41)**. The resonances for the starting material and the *ortho* and *para* substitution products **(75)** and **(76)** have been labelled sm, *o* and *p* respectively.

2.3.3 *Phenybutylamine* **(42)**

Reaction of phenylbutylamine **(42)** with chlorine in trifluorotoluene gave a mixture of the *ortho* and *para* chlorinated products **(77)** and **(78)** in quantitative yield. The products **(77)** and **(78)** were identified by comparison of their ^{1}H NMR spectra and/or melting points with literature data.[23]



42 **77** **78**

An *ortho*/*para* ratio of 60:40 was obtained by integration of the δ-methylene resonances in the ^{1}H NMR spectrum of the reaction mixture (Figure 2.12). The *ortho*/*para* ratio obtained was very similar compared to that for the chlorination of the substrate in carbon tetrachloride, where the value was 62:38 *ortho*/*para*.

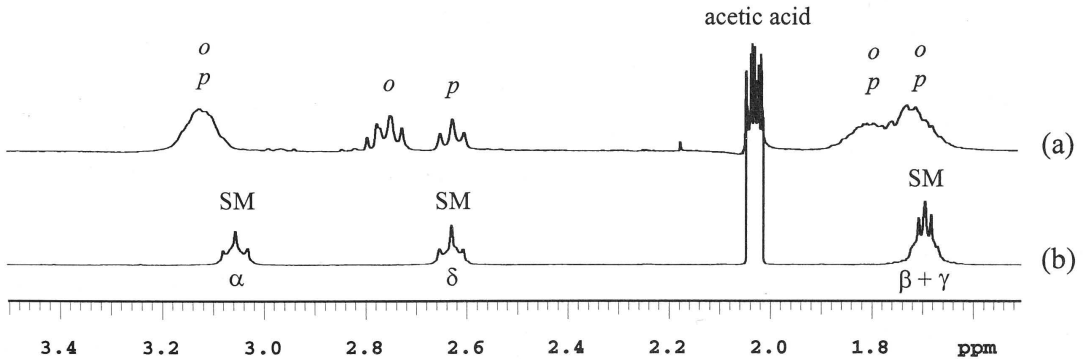
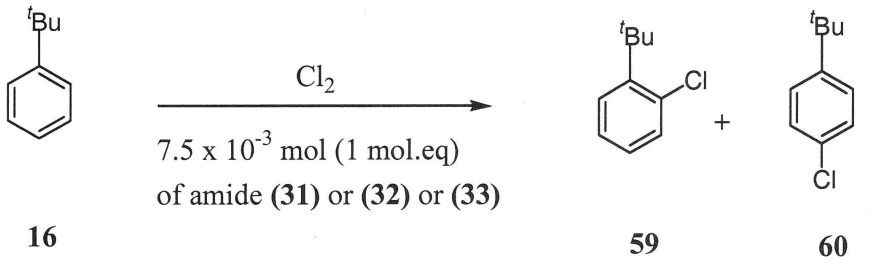


Figure 2.11 ^{1}H NMR spectra in acetic acid-d_4 of (a) the product mixture from chlorination of phenylbutylamine **(42)** in trifluorotoluene and (b) starting material **(42)**. The resonances for the starting material and the *ortho* and *para* substitution products **(77)** and **(78)** have been labelled sm, *o* and *p* respectively.

One of the limitations with the chlorination of phenylalkylamines in trifluorotoluene is that rate constants cannot be measured because there is formation of solids thereby creating heterogeneous conditions.

2.4 Competition reactions

It was previously seen that amides in particular and amines undergo rapid rates of aromatic chlorination in trifluorotoluene with only molecular chlorine present. It was determined that the rapid rate in aromatic chlorination could be attributed to the formation of the *O*-chloroimidate species,[23] which facilitated an intramolecular chlorination. The next step was to test whether or not these highly labile *O*-chloroimidate intermediates could catalyse the chlorination of aromatics that were known to chlorinate slowly under these condition, such as *t*-butylbenzene **(16)**, in an intermolecular manner.



16 **59** **60**

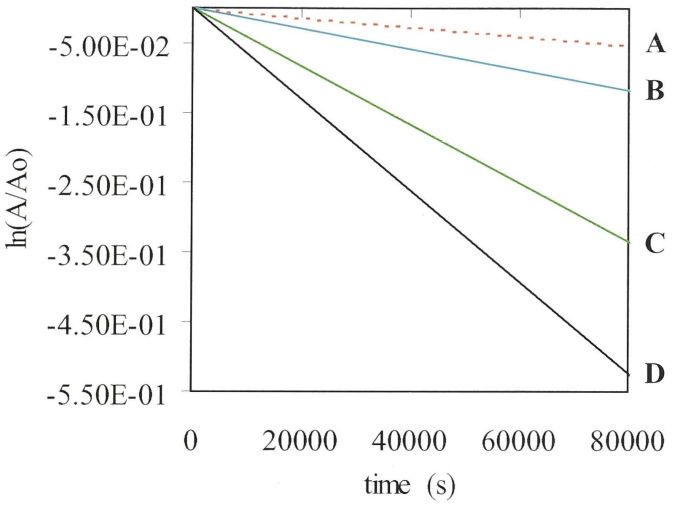
So *t*-butylbenzene **(16)** was treated with one molar equivalent of each of the amides **(33)**, **(32)** and **(31)** and chlorine solution (0.50 M) in trifluorotoluene at room temperature. The reactions were monitored in exactly the same way as that described for *t*-butylbenzene **(16)** earlier in this chapter *i.e.* run in a NMR tube with a Rototite® valve under solvent suppression conditions.[148] Because of the slow rates of aromatic chlorination observed, the reactions were analysed at approximately 24 hour intervals. The results for the experiments are presented in Table 2.6

Table 2.5 A summary of the pseudo-first order rate constants obtained for the aromatic chlorination of *t*-butylbenzene **(16)** in the presence of stoichiometric amounts of amides **(31)**, **(32)** and **(33)**.

Reaction	k (s^{-1})	**Rate Enhancement**
t-Butylbenzene **(16)**	6.48×10^{-7}	
t-Butylbenzene **(16)** + amide **(33)**	7.19×10^{-6}	11 x
t-Butylbenzene **(16)** + amide **(32)**	4.62×10^{-6}	7 x
t-Butylbenzene **(16)** + amide **(31)**	1.45×10^{-6}	2 x

The pseudo-first order rate constants for the chlorination of *t*-butylbenzene **(16)** are presented in Graph 2.12. The control experiment was the chlorination of *t*-butylbenzene **(16)** in the absence of any amide. The pseudo-first order rate constant for this reaction was 6.48×10^{-7} s^{-1}, which is quite slow (compared to rates observed for the amides). It can be seen from Table 2.5 that with only stoichiometric amounts of amide present, the rate of aromatic chlorination of *t*-butylbenzene **(16)** increases significantly. Phenylbutyramide **(33)** gives the greatest enhancement in rate for *t*-butylbenzene **(16)**, increasing the rate by a factor of 11. Phenylpropionamide **(32)** shows the next best increase in rate of chlorination of *t*-butylbenzene **(16)**, increasing it by a factor of 7. The shortest alkyl-chained amide phenyl acetamide **(31)** shows the least dramatic yet still modest increase in rate of chlorination of *t*-butylbenzene **(16)**, increasing the rate by a factor of 2.

The most likely explanation for the increase in rate of reaction of *t*-butylbenzene **(16)** in the presence of the amides **(31)**, **(32)** and **(33)** is that there is formation of the *O*-chloroimidate intermediates and they are attacked by both the tethered aromatic ring in an intramolecular fashion and the *t*-butylbenzene **(16)** aromatic ring in an intermolecular fashion.



Graph 2.12 A graphical representation of the increase in pseudo-first order rate constants for the chlorination of *t*-butylbenzene **(16)**. (A) *t*-butylbenzene **(16)** with no amide present, (B) *t*-butylbenzene **(16)** with 1 mol eq. of phenylacetamide **(31)**, (C) *t*-butylbenzene **(16)** with 1 mol eq. of phenylpropionamide **(32)**, (D) *t*-butylbenzene **(16)** with 1 mol eq. of phenylbutyramide **(33)**.

In summary, it has been demonstrated that trifluorotoluene is a suitable solvent to carry out electrophilic aromatic substitutions by exploiting the effect of amide and amine moieties. It has been demonstrated that both intramolecular chlorination and intermolecular chlorination work in trifluorotoluene. Increases in the rate of aromatic chlorination relative to simple alkylbenzenes were observed for all three phenylalkylamides **(31)**, **(32)** and **(33)**. Phenylbutyramide **(33)** and phenylpropionamide **(32)** showed increases of more than three orders of magnitude in the rate of aromatic chlorination, which from another perspective means that more than 1000 times less chlorine (or near stoichiometric amounts) could be used. Phenylalkylamines **(40)**, **(41)** and **(42)** all underwent aromatic chlorination in trifluorotoluene, and it was observed that the *o*/*p* ratio was governed by the alkyl chain length i.e. a shorter alkyl chain gave a greater amount of the *ortho* isomer.

Chapter Three

Effect of Cyclodextrins on Electrophilic Aromatic Halogenation

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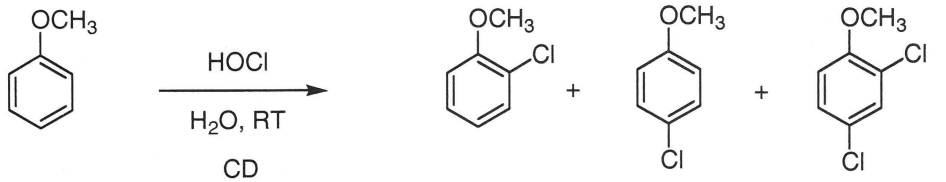
As discussed in the Introduction, the use of cyclodextrins as molecular reactors where they control the assembly of reactants to change the outcomes of chemical transformations has been well exploited.[101-103,122-132] The ability of cyclodextrins to increase, stabilise or retard the availability of active substances enables them to modify the reactivity of a large variety of molecules and improve the efficiency and selectivity of product formation.[132] Some of the advantages with this type of approach to chemical transformations and in particular towards aromatic halogenation are that the regioselectivity can be controlled and the reaction protocol in general, is highly simplified with reactions being performed in water. Given the synthetic utility of aromatic halides, environmentally friendly methods for their synthesis are vital. The advantages of using water as a reaction solvent are clear, particularly with the current emphasis on green chemistry techniques. For these reasons, reaction conditions which are not only aqueous, but use stoichiometric halogenating agent, and have controlled regiochemical outcomes, and hence produce less waste, are of increasing importance.

3.1 Aromatic Chlorination in Water

The classic study of aromatic halogenation in the presence of cyclodextrins by Breslow *et al.*[101-103] demonstrated that cyclodextrins could alter the regiochemical outcome of aromatic substitution. In their study of the hypochlorous acid chlorination of anisole **(45)**, they observed an increase in the *para*:*ortho* ratio with increasing amounts of cyclodextrin, with α-cyclodextrin **(48)** showing greater influence than β-cyclodextrin **(49)**. They reasoned that in the anisole-cyclodextrin inclusion complex, the *ortho* positions are shielded from attack by the cyclodextrin, while the *para* position is still accessible to solvent and reagents.

Accordingly in the present work, chlorination studies of anisole **(45)** and a range of related compounds were undertaken. The chlorination of anisole was carried out as previously reported by Breslow *et al.* In this case 0.1 mmol of anisole **(45)** was treated with 10 eq of hypochlorous acid in water (Scheme 3.1). The reactions were carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of a cyclodextrin. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.1. These were determined through integration of key resonances (Table 3.2) that were assigned based on comparison with the spectra of authentic samples.



45 **46** **47** **77**

Scheme 3.1

The results were consistent with the literature in that both α and β-cyclodextrin decreased the proportion of *ortho* chlorinated product **(46)**, more so with α-cyclodextrin. In our experiments small amounts of 2,4-dichloroanisole **(77)** were also observed, but not to an extent that affects the general conclusion that the cyclodextrin inclusion reduces *ortho* chlorination, so this concurs with Breslow's suggestion that the *ortho* position is shielded.

Table 3.1 Products from the chlorination of anisole **(45)** with and without *n*-octanol **(78)**.

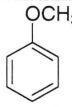
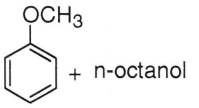
Substrate	Cyclodextrin (CD)	Product Ratios (%)			
		SM	**(46)**	**(47)**	**(77)**
 **45**	-	0	29	52	19
	α-CD	0	7	83	10
	β-CD	0	21.5	75	3.5
 **45**	-	0	31	62	7
	α-CD	0	24	66	10
	β-CD	0	21.5	72.5	6

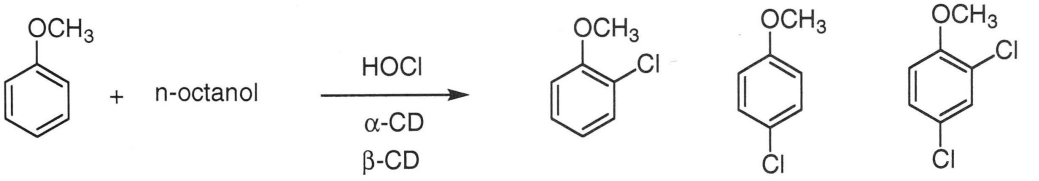
Table 3.2 NMR signals used for determining product ratios for reactions of compounds **(45)**, **(52)** and **(56)**

Compound	Solvent	Spectral Data[A]	Reference
(45)	$CDCl_3$	7.22 (2H, m, H3, H5), 6.91–6.80 (3H, m, H2, H4, H6), 3.77 (3H, s, OCH_3)	B
(46)	$CDCl_3$	7.35 (1H, dd, *J* 7.5, 1.5 Hz, H3), 6.88 (1H, m, H4), 7.22 (1H, m, H5), 6.92 (1H, dd, *J* 8.5, 1.5 Hz, H6), 3.89 (3H, s, OCH_3)	B
(47)	$CDCl_3$	6.82 (2H, d, *J* 9.0 Hz, H2, H6), 7.23 (2H, d, *J* 9.0 Hz, H3, H5), 3.80 (3H, s, OCH_3)	B
(77)	$CDCl_3$	7.35 (1H, d, *J* 2.5 Hz, H3), 7.18 (1H, dd, *J* 9.0, 2.5, H5), 6.84 (1H, d, J 9.0 Hz, H6), 3.87 (3H, s, OCH_3)	54
(52)	d_6-DMSO	7.54 (2H, d, *J* 7.5 Hz, H2, H6), 7.26 (2H, t, *J* 7.5 Hz, H3, H5), 7.00 (1H, t, *J* 7.5 Hz, H4), 2.02 (3H, s, $NHCOCH_3$)	B
(56)	$CDCl_3$	7.38 (2H, m, H3, H5), 7.24 (1H, m, H4), 7.09 (2H, m, H2, H6), 2.28 (3H, s, $COCH_3$)	B
(86)	$CDCl_3$	7.54 (1H, dd, *J* 8.0, 1.5 Hz, H6), 7.27 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, H5), 6.90 (1H, dd, *J* 8.5, 1.5 Hz, H3), 6.84 (1H, ddd, *J* 8.5, 7.5, 1.5 Hz, H4), 3.89 (3H, s, OCH_3)	B
(89)	d_6-DMSO	7.61 (1H, d, *J* 7.5, 1.5 Hz, H6), 7.33 (1H, td, *J* 7.5, 1.5 Hz, H5), 7.10 (1H, td, *J* 7.5, 1.5 Hz, H4), 2.06 (3H, s, $NHCOCH_3$)	158
(92)	$CDCl_3$	7.60 (1H, dd, *J* 8.5, 1.5 Hz, H6), 7.32 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, H5), 7.13 (1H, m, H3), 7.12 (1H, m, H4), 2.34 (3H, s, $COCH_3$)	159
(87)	$CDCl_3$	6.70 (2H, d, *J* 9.0 Hz, H2, H6), 7.29 (2H, d, *J* 9.0 Hz, H3, H5), 3.79 (3H, s, OCH_3)	B
(90)	d_6-DMSO	7.53 (2H, d, *J* 9.0 Hz, H3, H5), 7.43 (2H, d, *J* 9.0 Hz, H2, H6), 2.02 (3H, s, $NHCOCH_3$)	B
(93)	$CDCl_3$	7.46 (2H, d, *J* 9.0 Hz, H3, H5), 6.96 (2H, d, *J* 9.0 Hz, H2, H6), 2.27 (3H, s, $COCH_3$)	160
(88)	$CDCl_3$	7.65 (1H, d, *J* 2.5 Hz, H3), 3.87 (3H, s, OCH_3)	54
(91)	d_6-DMSO	7.72 (1H, d, *J* 2.1 Hz, H3), 2.11 (3H, s, $NHCOCH_3$)	161

[A] Discrete signals were not observed for all resonances; those which could not be unambiguously assigned are not shown.
[B] Spectrum of an authentic sample.

A further experiment was performed to see what effect a competing guest would have on the chlorination of anisole. It was reasoned that with the use of a competitive guest to displace the anisole **(45)**, it would be possible to nullify the effect imparted by the cyclodextrin through inclusion. *n*-Octanol **(78)** was chosen as the displacing guest because it has a much higher binding constant with both α- and β-cyclodextrin compared to anisole **(45)**. The binding constants of anisole **(45)** have been noted in the literature and are 269 and 139 M^{-1} with α- and β-cyclodextrin respectively; this is much lower than the binding constants of *n*-octanol **(78)** which are 7800 and 2100 M^{-1} with α- and β-cyclodextrin respectively.[117]

The chlorination of anisole **(45)** was carried out as previously mentioned in a similar manner to that reported by Breslow *et.al.* In this case 0.1 mmol of anisole **(45)** was treated with 10 eq of hypochlorous acid in water. The reactions were carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) or no cyclodextrin and in the presence of 10 eq *n*-octanol (Scheme 3.2). After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.1. As before, these were determined through integration of key resonances (Table 3.2) that were assigned based on comparison with the spectra of authentic samples.



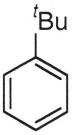
45 **78** **46** **47** **77**

Scheme 3.2

From Table 3.1 it can be suggested that the *n*-octanol **(78)** displaces the anisole **(45)** from the cyclodextrin cavity in the case involving α-cyclodextrin **(48)** because there is a substantial reduction of effect of the cyclodextrin. The amount of *para* product **(47)** is

decreased from 83 to 66%. In the case of β-cyclodextrin **(49)** it seems there is very little displacement of anisole **(45)** if any, because the ratio of products is almost identical when *n*-octanol **(78)** is present or not. This result is somewhat surprising considering the large difference in the binding constants between *n*-octanol **(78)** and anisole **(45)**, where the displacement of anisole **(45)** would almost certainly be expected to take place. The control experiment with *n*-octanol **(78)** gives an almost similar amount of *ortho* product **(46)** compared to the analogous control experiment in the absence of *n*-octanol. More *para* product **(47)** and less dichlorinated product **(77)** is also observed when *n*-octanol is present.

Chênevert *et.al.*[126] showed that acetanilide **(52)** could be successfully chlorinated in water. Bearing in mind and considering the ease of the reaction protocol and the selectivity of chlorination in the presence of cyclodextrins, this prompted an investigation into the aromatic chlorination of other aromatic compounds such as *t*-butylbenzene **(16)**, naphthalene **(79)**, 2-methoxynaphthalene **(80)**, 2-methylnaphthalene **(81)** and anthracene **(82)**.



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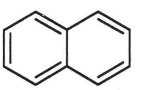

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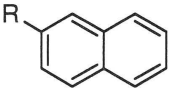
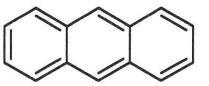


R = OMe **80**
= Me **81**



82

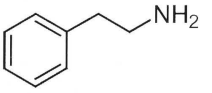
The chlorination of compounds **(16)**, **(79)**, **(80)**, **(81)** and **(82)** was carried out as previously mentioned in a similar manner to that described for anisole **(45)**. 0.1 mmol of substrate was treated with 10 eq of hypochlorous acid in water. The reactions were carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.). After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy.

Initially, there was difficulty in obtaining homogenous solutions of the compounds in water due to their non-polar and hence insoluble nature. For this reason no control experiments were performed. The compounds **(16)**, **(79)**, **(80)** and **(81)** all failed to chlorinate to an appreciable level. Only anthracene **(82)** when treated with hypochlorous acid showed a very small amount of reaction with less than 5% of products other than starting material detected by ^{1}H NMR. It seems that the compounds being tested for aromatic chlorination perhaps require further activation or at least require a polar functional group to aid in the solubility in water.

3.2 Modified Cyclodextrins

While the natural cyclodextrins are themselves of interest as molecular hosts, much of their utility in chemistry derives from their modification.[121,162] In terms of functional groups with the potential for catalytic activity, the naturally occurring cyclodextrins are somewhat limited in utility, with only hydroxyl groups present. It was envisaged that with the appropriate functional group the cyclodextrins might act as better catalysts in the chlorination of aromatic substrates.

In Chapter 2 it was shown that aromatics functionalised with amine and amide moieties underwent chlorination in an intramolecular manner. For example phenylethylamine **(40)** when treated with chlorinating agent gave predominantly one chlorinated isomer through formation of the *N*-chloro species. Earlier in this chapter it was also shown that aromatics such as anisole **(45)** underwent selective chlorination in the presence of cyclodextrins by being included in the cyclodextrin cavity. So it was thought that these two approaches could be hybridised in such a way as to design a cyclodextrin that allowed formation of the *N*-chlorospecies (Figure 3.1). An amino modified cyclodextrin **(83)** was chosen for this purpose and was synthesised and used accordingly for studies of aromatic chlorination of anisole **(45)**.



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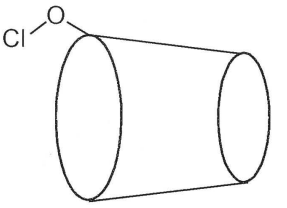
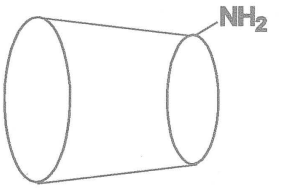


51



83

Figure 3.1 The cyclodextrin chosen for chlorination studies with anisole **(45)** was an amino cyclodextrin **(83)**, which combined both an amine to allow the formation of an *N*-chloro intermediate, and a cyclodextrin to allow inclusion of the substrate and have it in close proximity to the halogenating species.

The chlorination of anisole **(45)** was carried out in a manner to that described for chlorination of anisole with unmodified cyclodextrins, where anisole **(45)** (0.1 mmol) was treated with hypochlorous acid (10 mol. equiv.) in water. The reactions were carried out at room temperature in the presence of either α-aminocyclodextrin **(84)** or β-aminocyclodextrin **(85)** (10 mol. equiv.) and were analysed after 1 hour. The analysis showed only minute consumption of the starting material so the reaction was allowed to proceed for 24 hours. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy (Table 3.2) and the results are presented in Table 3.3.

Table 3.3 Products of chlorination of anisole **(45)** in the presence of amino cyclodextrins.

Substrate	Cyclodextrin (CD)	Product Ratios (%)			
		SM	**(46)**	**(47)**	**(77)**
anisole	-	0	48	32	20
	α-CD-NH_2	40	4	56	0
	β-CD-NH_2	32	14.5	53.5	0

In the reactions carried out in the presence of amino-cyclodextrins there was a noticeable amount of starting material left even after 24 hours. This indicated that the modified cyclodextrins were retarding the rate of aromatic chlorination of anisole **(45)**. The slower rate of aromatic chlorination was suggested to occur due to the formation of the *N*-chloro species. So in a separate experiment hypochlorous acid was treated with varying concentrations of amine and the loss of absorbance monitored by UV-visible spectroscopy. It was found that hypochlorous acid reacted with amines in a 1:1 ratio (Table 28, Appendix I). So it is believed that the *N*-chlorospecies indeed does form, but surprisingly it does not react with the anisole **(45)** as quickly as reactions in the presence of un-modified cyclodextrins or the control experiment. This suggests that the *N*-chloro species has a much higher stability than that observed for the previously studied *N*-chloro intermediates in Chapter 2. The effect of the cyclodextrins should also be noted where predominantly the *para* isomer **(47)** was formed in the presence of cyclodextrins compared to the control reaction. α-Cyclodextrin has a greater effect than β-cyclodextrin, which is analogous to the previous results involving unmodified cyclodextrins.

3.3 Aromatic Bromination in Water

Due to the limited success with aromatic chlorination in the presence of cyclodextrins, aromatic brominations were undertaken. Bromination of aromatic compounds in the

presence of cyclodextrins has been noted in the literature.[134] Tee and Bennett investigated the effects of cyclodextrins on the bromination of anisole **(45)** with bromine/KBr in water. In this system the cyclodextrins did not alter the regioselectivity. Instead, the cyclodextrins retarded the rate of aromatic bromination and it was suggested to occur firstly, due to the inclusion of both the substrate and brominating agent and secondly, due to the formation of a complex between the cyclodextrins and the tribromide ion. Muathen *et al.*[147] recently showed that a range of aromatic compounds could be brominated with the use of pyridinium dichlorobromate **(55)** in aqueous methanol.

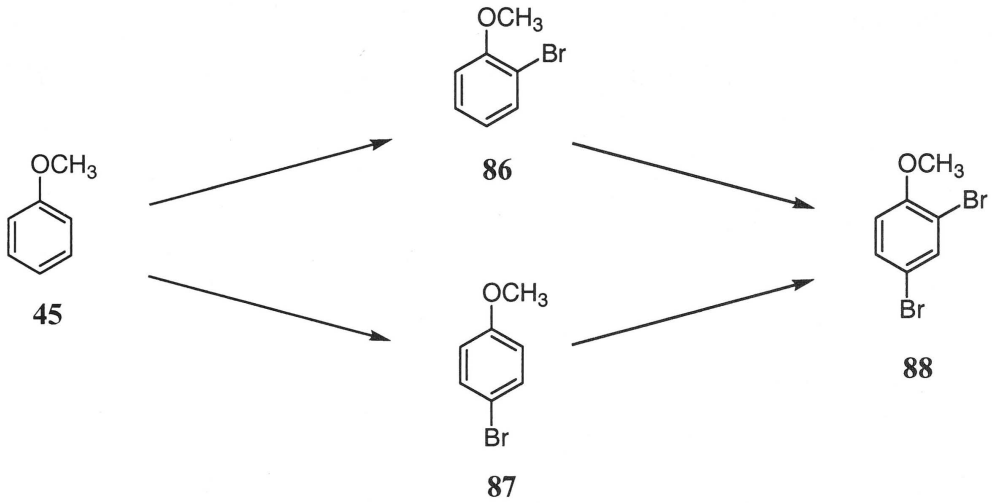
In light of the lack of regiocontrol for the aqueous bromination of aromatics, the recent account of the use of pyridinium dichlorobromate **(55)** prompted the investigation of the effect of cyclodextrins with this reagent. The substrates chosen for this study were anisole **(45)** and acetanilide **(52)**, in order to make direct comparisons to the chlorination of these compounds. Phenyl acetate **(56)** was chosen on the basis that the ester is less reactive. The methyl-substituted anisole **(57)** and acetanilide **(58)** were selected, firstly, on the basis that the ether and amide are more reactive towards aromatic substitution and secondly, this would allow an insight into the effect of cyclodextrins towards aromatic substitutions on more complicated systems.

3.3.1 Anisole **(45)**

Anisole **(45)** (0.2 mmol) was treated with pyridinium dichlorobromate **(55)** (1.1 mol. equiv.), in water containing methanol (1% v/v). The reaction was carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of a cyclodextrins (Scheme 3.3). After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.4. These were determined through integration of key resonances (Table 3.2) that were assigned based on comparison with the spectra of authentic samples.

Table 3.4 Products of the bromination of anisole **(45)**

Cyclodextrin (CD)	Product Ratios (%)			
	(45)	**(86)**	**(87)**	**(88)**
-	0	12	73	15
α-CD	0	2	94	4
β-CD	0	6	86	8



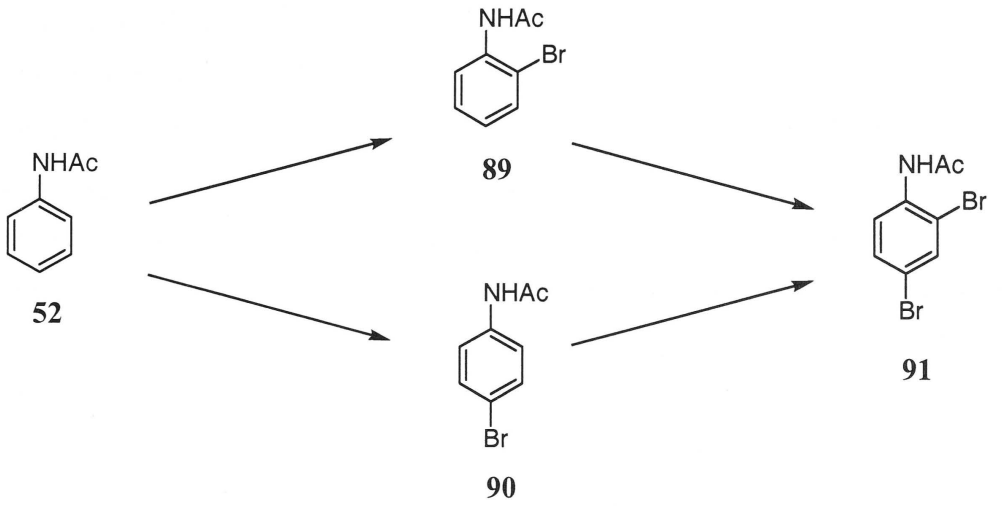
Scheme 3.3

It can be seen that for the reaction between anisole **(45)** and 1.1 equiv. of the brominating agent both α- and β-cyclodextrin change the ratios of the formation of the monobrominated products **(86)** and **(87)** in favour of the *para*-substituted isomer **(87)**. The greatest effect is observed with α-cyclodextrin where the *ortho*/*para* ratio is 2/94 compared to β-cyclodextrin where the *ortho*/*para* ratio is 6/86; both showing considerably more *para* product **(87)** compared to the reaction in the absence of cyclodextrins where the *ortho*/*para* ratio was 12/73. It is thus apparent that the cyclodextrins limit *ortho* bromination of anisole **(45)**, presumably through the formation of inclusion complexes restricting the access of the brominating agent, in a manner that is directly analogous to the effect of cyclodextrins on the chlorination reported

previously.[101-103] The cyclodextrins also limit the extent of formation of the dibromide **(88)**, which is formed in a noticeable quantity in the control experiment. As was the case before, it is α-cyclodextrin **(48)** that has the most effect, reducing the formation of the dibromide **(88)** from 15 to 4%, and β-cyclodextrin **(49)** reduces the formation of the dibromide **(88)** from 15 to 8%. The formation of the dibromide **(88)** occurs presumably via the corresponding monobromides **(86)** and **(87)** (Scheme 3.3). It seems likely that the effect imparted by the cyclodextrins (limiting the formation of the dibromide **(88)**) is due to the cyclodextrins retarding further bromination of the *para*-isomer **(87)**, by blocking the 2-position. The net result of these effects for α-cyclodextrin and β-cyclodextrin is an increase in the yield of the *para* product from 73 to 94% and 73 to 86% respectively, and a substantial decrease in the quantity of the corresponding by-products, from 27 to 6% and from 27 to 14% respectively.

3.3.2 Acetanilide **(52)**

Acetanilide **(52)** (0.2 mmol) was treated with pyridinium dichlorobromate **(55)** (1.1 mol. equiv.), in water containing methanol (1% v/v). The reaction was carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of any cyclodextrin. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.5. These were determined through integration of key resonances (Table 3.2) that were assigned based on comparison with the spectra of authentic samples.



Scheme 3.4

Table 3.5 Products of the bromination of acetanilide **(52)**

Cyclodextrin (CD)	Product Ratios (%)			
	(52)	**(89)**	**(90)**	**(91)**
-	0	42	55	3
α-CD	0	0	98	2
β-CD	0	21	79	0

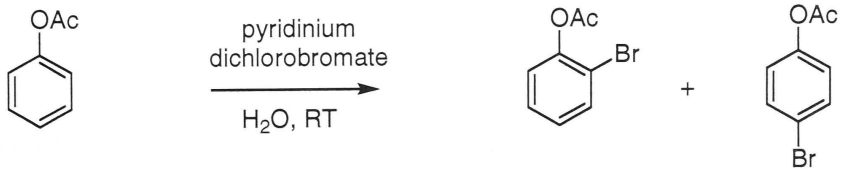
It can be seen that for the reaction between acetanilide **(52)** and 1.1 equiv. of the brominating agent both α- and β-cyclodextrin change the ratios of the formation of the monobrominated products **(89)** and **(90)** in favour of the *para*-substituted isomer **(90)**. The greatest effect is observed with α-cyclodextrin where only the *para* isomer **(90)** is formed compared to β-cyclodextrin where the *ortho*/*para* ratio is 21/79; both showing considerably more *para* product **(90)** compared to the reaction in the absence of cyclodextrins where the *ortho*/*para* ratio was 42/55.

It is thus apparent that the cyclodextrins limit *ortho* bromination of acetanilide **(52)**, presumably through the formation of inclusion complexes restricting the access of the brominating agent, in a manner that is directly analogous to the effect of cyclodextrins on

the bromination of anisole **(45)**. The cyclodextrins also limit the extent of formation of the dibromide **(91)**, which is formed in a small amount in the control experiment. β-Cyclodextrin has the most effect, reducing the formation of the dibromide **(91)** from 3 to 0%, and α-cyclodextrin reduces the formation of the dibromide **(91)** from 3 to 2%. The formation of the dibromide **(91)** occurs in a similar manner to that described for anisole **(45)**, presumably via the corresponding monobromides **(89)** and **(90)** following exactly the same scheme described for anisole (Scheme 3.6). It seems likely that the effect imparted by the cyclodextrins (limiting the formation of the dibromide **(91)**) is due to the cyclodextrins retarding further bromination of the *para*-isomer **(90)**, by blocking the 2-position. The net result of these effects for α-cyclodextrin and β-cyclodextrin is an increase in the yield of the *para* product from 55 to more than 95% and 55 to 79% respectively, and a decrease in the quantity of the corresponding by-products.

3.3.3 Phenylacetate **(56)**

Phenylacetate **(56)** (0.2 mmol) was treated with pyridinium dichlorobromate **(55)** (1.1 mol. equiv.), in water containing methanol (1% v/v) (Scheme 3.5). The reaction was carried out at room temperature for initially 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of any cyclodextrin. The reaction time was increased to 24 hours because very little extent of reaction was observed after the initial time. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.6. These were determined through integration of key resonances (Table 3.2) that were assigned based on comparison with the spectra of authentic samples.



56 **92** **93**

Scheme 3.5

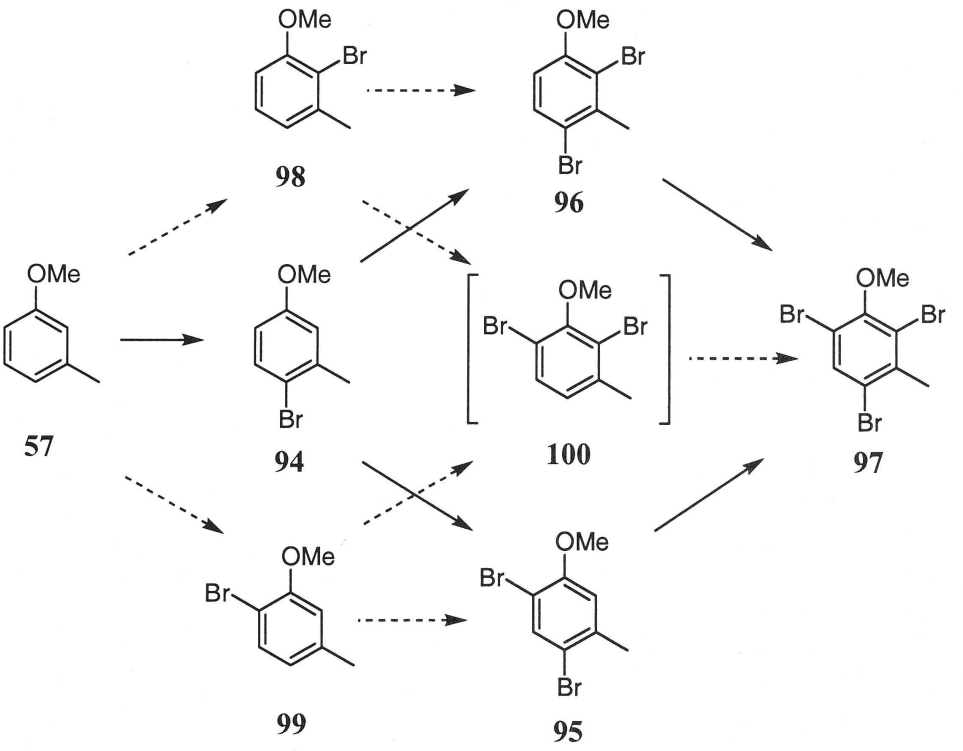
For the reaction between acetanilide **(56)** and 1.1 equiv. of the brominating agent both α- and β-cyclodextrin did not alter the ratios of products. The control reaction afforded predominantly the *para* isomer **(93)** and starting material **(56)** just as the reactions in the presence of cyclodextrins did. In general, phenylacetate **(56)** reacted to a much lesser extent than the previously studied aromatics **(45)** and **(52)**, even after much longer reaction times and only the mono brominated products **(92)** and **(93)** were produced i.e. there was no evidence of formation of a dibromide. It is somewhat surprising to see that in the presence of β-cyclodextrin there was a significant retardation in the rate of aromatic bromination, which was not apparent for reaction with α-cyclodextrin or the control reaction.

Table 3.6 Products of the bromination of acetanilide **(56)**

Cyclodextrin (CD)	Product Ratios (%)		
	(56)	**(92)**	**(93)**
-	41	2	57
α-CD	40	2	58
β-CD	77	1	22

3.3.4 3-Methylanisole **(57)**

3-Methylanisole **(57)** (0.2 mmol) was treated with varying amounts of pyridinium dichlorobromate **(55)** (0.6, 1.1 and 2.2 mol. equiv.), in water containing methanol (1% v/v) (Scheme 3.6). The reaction was carried out at room temperature for 1 hour, in the presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of any cyclodextrin. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.7. These were determined through integration of key resonances (Table 3.8) that were assigned based on comparison with the spectra of authentic samples.



Scheme 3.6

Table 3.7 Products of the bromination of 3-methylanisole **(57)**

Cyclodextrin	Reagent	Product Ratios (%)				
(CD)	(mol.equiv.)	**(57)**	**(94)**	**(96)**	**(95)**	**(97)**
-	0.6	50	23	12	14	1
α-CD	0.6	40	42	8	9	1
β-CD	0.6	36	59	3	2	0
-	1.1	23	37	19	20	1
α–CD	1.1	12	46	18	21	1
β-CD	1.1	4	86	5	5	0
-	2.2	0	30	29	34	7

Table 3.8 NMR signals used for determining product ratios of reactions of **(57)** and **(58)**

Compound	Solvent	Spectral Data[A]	Reference
(57)	CD_3OD	7.11 (1H, t, *J* 8.0 Hz, H5), 6.71 (2H, m, H4, H6), 6.66 (1H, m, H2), 3.73 (3H, s, OCH_3), 2.28 (3H, s, $ArCH_3$)	B
(58)	CD_3OD	7.35 (1H, br s, H2), 6.90 (1H, br d, *J* 8.0 Hz, H4), 7.15 (1H, t, *J* 8.0 Hz, H5), 7.30 (1H, br d, *J* 8.0 Hz, H6)	B
(94)	CD_3OD	7.35 (1H, d, *J* 8.5 Hz, H5), 6.83 (1H, d, *J* 3.0 Hz, H2), 6.63 (1H, dd, *J* 8.5, 3.0 Hz, H6), 3.74 (3H, s, OCH_3), 2.32 (3H, s, $ArCH_3$)	163
(95)	CD_3OD	7.60 (1H, s, H6), 6.69 (1H, s, H3)	B
(96)	CD_3OD	7.49 (1H, d, *J* 9.0 Hz, H5), 6.80 (1H, d, *J* 9.0 Hz, H6)	B
(97)	CD_3OD	7.79 (1H, s, H5)	B
(101)	CD_3OD	7.47 (1H, d, *J* 2.5 Hz, H2), 7.41 (1H, d, *J* 8.5 Hz, H5), 7.28 (1H, dd, *J* 8.5, 2.5 Hz, H6)	164
(102)	CD_3OD	7.60 (1H, br s, H6), 7.76 (1H, s, H3)	165
(103)	CD_3OD	7.53 (1H, d, J 8.5 Hz, H5)	165
(104)	CD_3OD	7.87 (1H, s, H5)	165
(X)	CD_3OD	7.12 (1H, ddq, *J* 8.5, 3.0, 0.5 Hz), 7.68 (1H, d, *J* 8.5 Hz)	

[A] Discrete signals were not observed for all resonances; those which could not be unambiguously assigned are not shown.
[B] Spectrum of an authentic sample.

In the reaction of 3-methylanisole **(57)**, unreacted starting material and the monobromide **(94)**, dibromides **(95)** and **(96)**, and tribromide **(97)** accounted for at least 95 mol% of the product mixtures. This was determined by analysis of ^{1}H NMR spectra and particularly through comparison of the integrations of all the methyl proton resonances relative to those of the aromatic protons.

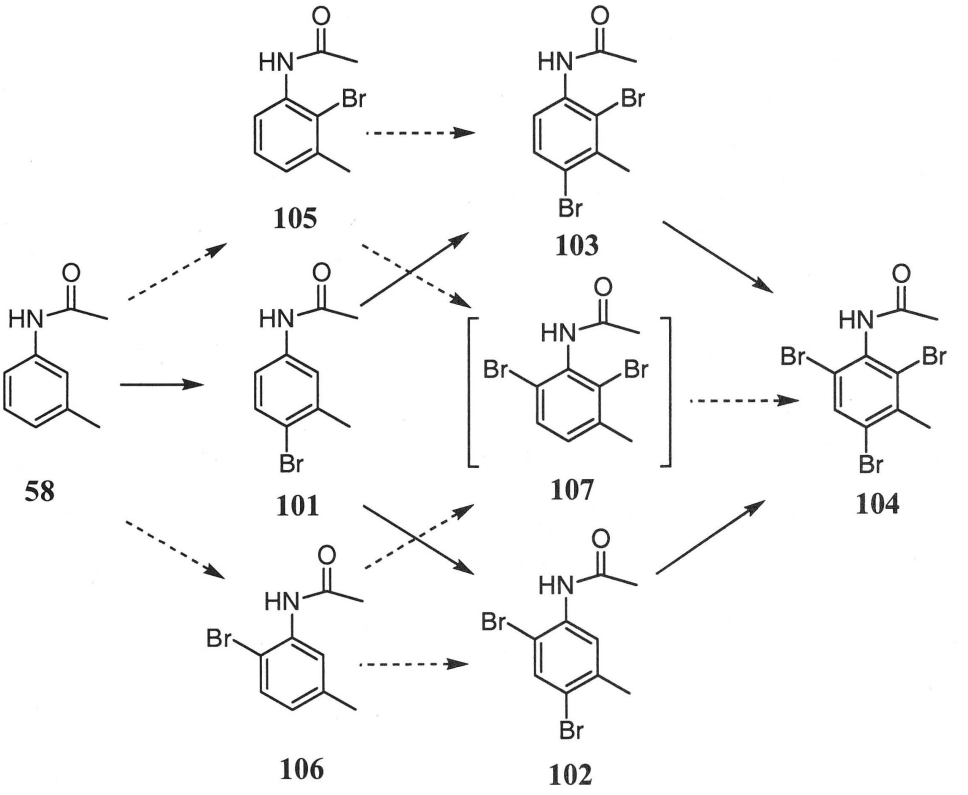
In the control experiments (Table 3.7) there was a considerable yield of the dibrominated products **(95)** and **(96)**. It appears that monobromination seems to activate the system to further reaction. Presumably, the combination of the methoxy and methyl substituents seems to perturb the balance of resonance and inductive effects normally seen with a bromo group. Significant quantities of **(98)**, **(99)** and **(100)** do not build up in the reactions of 3-methylanisole **(57)**. It has been suggested that the bromides **(98)**, **(99)** and **(100)** are unusually reactive, and once formed react further to give **(95)**, **(96)** and subsequently **(97)** as shown in Scheme 3.8, but another contributing factor may be that, perhaps there is selectivity towards bromination *para* to the methoxy substituent.

Both cyclodextrins afford a much greater proportion of the monobrominated product **(94)** and limit the extent of reaction to form the dibrominated products **(95)** and **(96)** and the tribrominated product **(97)**. The effect of the cyclodextrins is to prevent bromination adjacent to the methoxy group, in a similar manner to that seen with anisole **(45)**, but in the methylated system discussed here, β-cyclodextrin has the greatest effect. When 1.1 mol. equiv of the brominating agent was used, the yield of the monobrominated product **(94)** was increased slightly from 37 to 46% with α-cyclodextrin and more dramatically from 37 to 86% with β-cyclodextrin, moreover there was a substantial decrease in the quantity of the corresponding by-products from 63 to 14%.

3.3.5 3-Methylacetanilide **(58)**

3-Methylacetanilide **(58)** (0.2 mmol) was treated with varying amounts of pyridinium dichlorobromate **(55)** (0.6 and 1.1 mol. equiv.), in water containing methanol (1% v/v) (Scheme 3.7). The reaction was carried out at room temperature for 1 hour, in the

presence of either α- or β-cyclodextrin (10 mol. equiv.) and a control experiment was carried out in the absence of cyclodextrins. After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 3.9. These were determined through integration of key resonances (Table 3.8) that were assigned based on comparison with the spectra of authentic samples.



Scheme 3.7

In the reaction of 3-methylacetanilide **(58)**, unreacted starting material and the monobromide **(101)**, dibromides **(102)** and **(103)**, tribromide **(104)** and an unidentified product **(X)** accounted for at least 95 mol% of the product mixtures. This was determined by analysis of ^{1}H NMR spectra and particularly through comparison of the integrations of all the methyl proton resonances relative to those of the aromatic protons.

Table 3.9 Products of the bromination of 3-methylacetanilide **(58)**

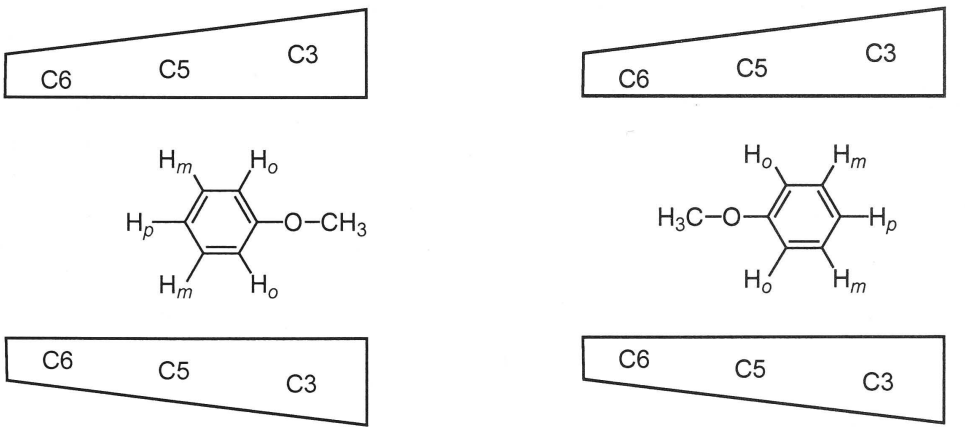
Cyclodextrin	Reagent	Product Ratios (%)					
(CD)	(mol.equiv.)	**(58)**	**(101)**	**(103)**	**(102)**	**(104)**	**(X)**
-	0.6	51	36	8	5	0	0
α-CD	0.6	43	48	6	3	0	0
β-CD	0.6	44	48	5	3	0	0
-	1.1	12	39	9	7	20	13
α–CD	1.1	5	64	9	6	13	3
β-CD	1.1	3	72	7	4	1	13

When 3-methylacetanilide **(58)** was treated with either 0.6 or 1.1 mol. equiv of brominating agent very similar results were obtained to those with 3-methylanisole **(57)**. In the control reactions there was a considerable yield of the dibromo compounds **(102)** and **(103)** and the tribromo compound **(104)**. When the reactions were performed in the presence of cyclodextrins there was a substantial reduction in the formation of the dibromides **(102)** and **(103)** and an increase in yield of the monobromide **(101)**, with β-cyclodextrin having the greatest effect. Both these results (from control reactions and those in the presence of cyclodextrins) complement those obtained for the analogous anisole derivative **(57)**.

In summary, for the reactions on the monosubstituted aromatics **(45)**, **(52)** and **(56)** carried out in the absence of a cyclodextrin, the formation of only small amounts of the dibromides **(88)** and **(91)** from anisole **(45)** and acetanilide **(52)**, respectively, relative to the yields of the corresponding monobromides **(86)**, **(87)**, **(89)** and **(90)**, indicates that the bromo substituents of **(86)**, **(87)**, **(89) and (90)** reduce the reactivity of these systems towards further aromatic substitution. This deactivation is typical of halogens and is greatest with the acetanilides **(52)**, **(89)** and **(90)**. By contrast the yields of the dibromides **(95)**, **(96)**, **(102)** and **(103)** from methylanisole **(57)** and methylacetanilide **(58)** are more

substantial (Table 3.8 and Table 3.9), particularly with the anisole **(57)** where monobromination appears to activate the system to further reaction.

It seems likely that a major contributing factor to the regiocontrol provided by the cyclodextrins derives from complexation of the substrates **(45)**, **(52)**, **(57)** and **(58)** in such a way as to restrict access of the reagent adjacent to the methoxy and acetamido substituents. Such shielding is reflected in 2D ROESY spectra of mixtures of anisole **(45)** and α- and β-cyclodextrin (Figures 3.2 and 3.3, respectively), which both show NOEs between the resonances of the *ortho* hydrogens of the substrate and the cyclodextrin C3 and C5 hydrogen resonances. It can therefore be concluded that anisole includes into the cyclodextrin cavity and interactions between the *ortho* and *meta* hydrogens with the cyclodextrin hydrogens are present, while no NOE interaction is observed for the *para* hydrogen. The exact orientation of the guest inside the cyclodextrin cavity [shown below]) cannot be determined. 2D ROESY spectra of mixtures of the other substrates **(52)**, **(57)** and **(58)** with cyclodextrins also show NOEs between the resonances of the substrates and the cyclodextrin hydrogens. These show that the substrates are included in the cyclodextrins in aqueous solution but further interpretation of the data is impractical in these cases due to overlapping resonances and changes in the chemical shifts of the substrate resonances induced by the cyclodextrins.



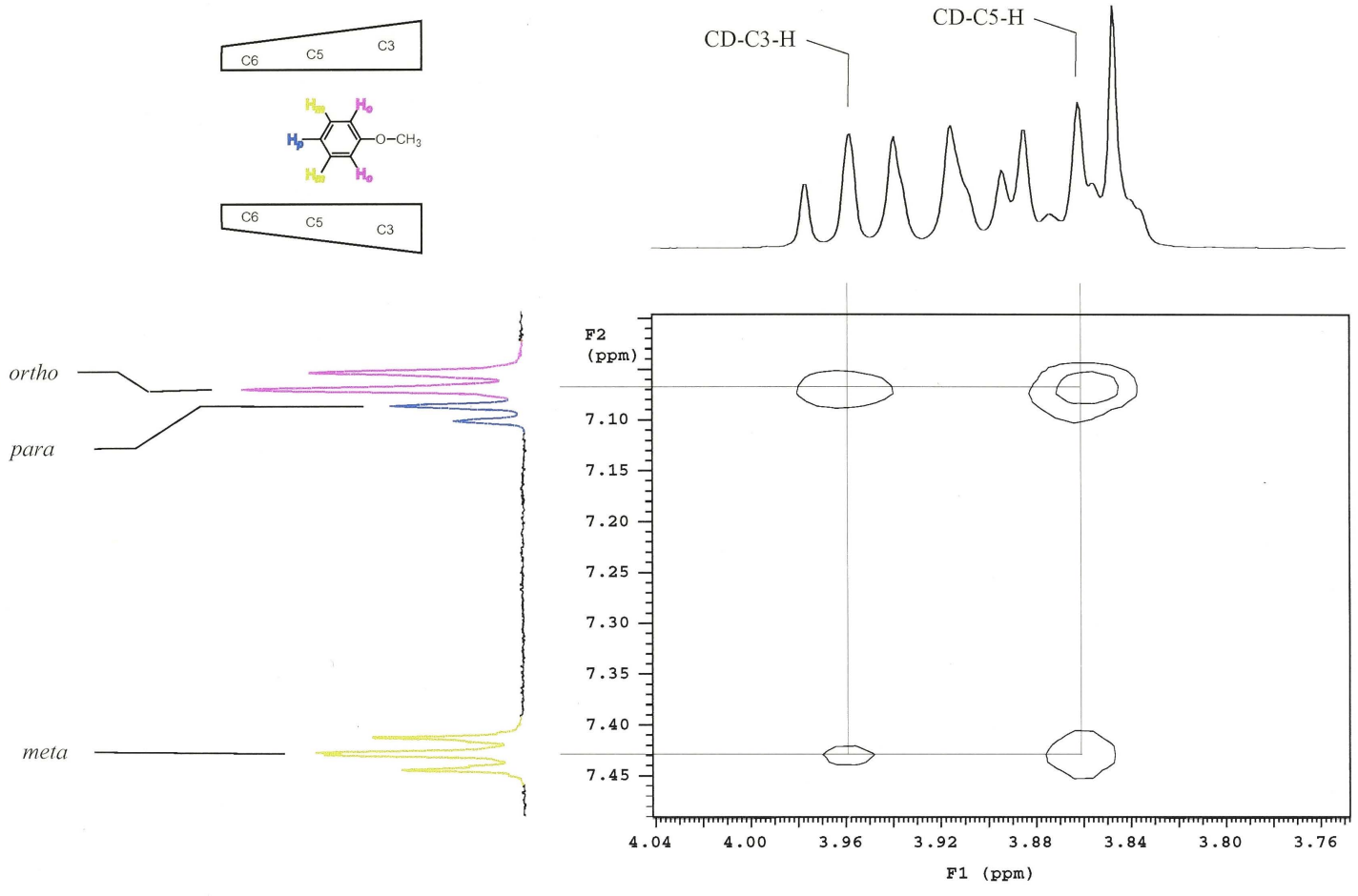


Figure 3.2 A portion of the ROESY spectrum (500 MHz) recorded of a solution of anisole **(45)** (10 mM) and a-cyclodextrin (10 mM) in D_2O, showing interactions between resonances of the cyclodextrin (x-axis) and those of the anisole **(45)** (y-axis).

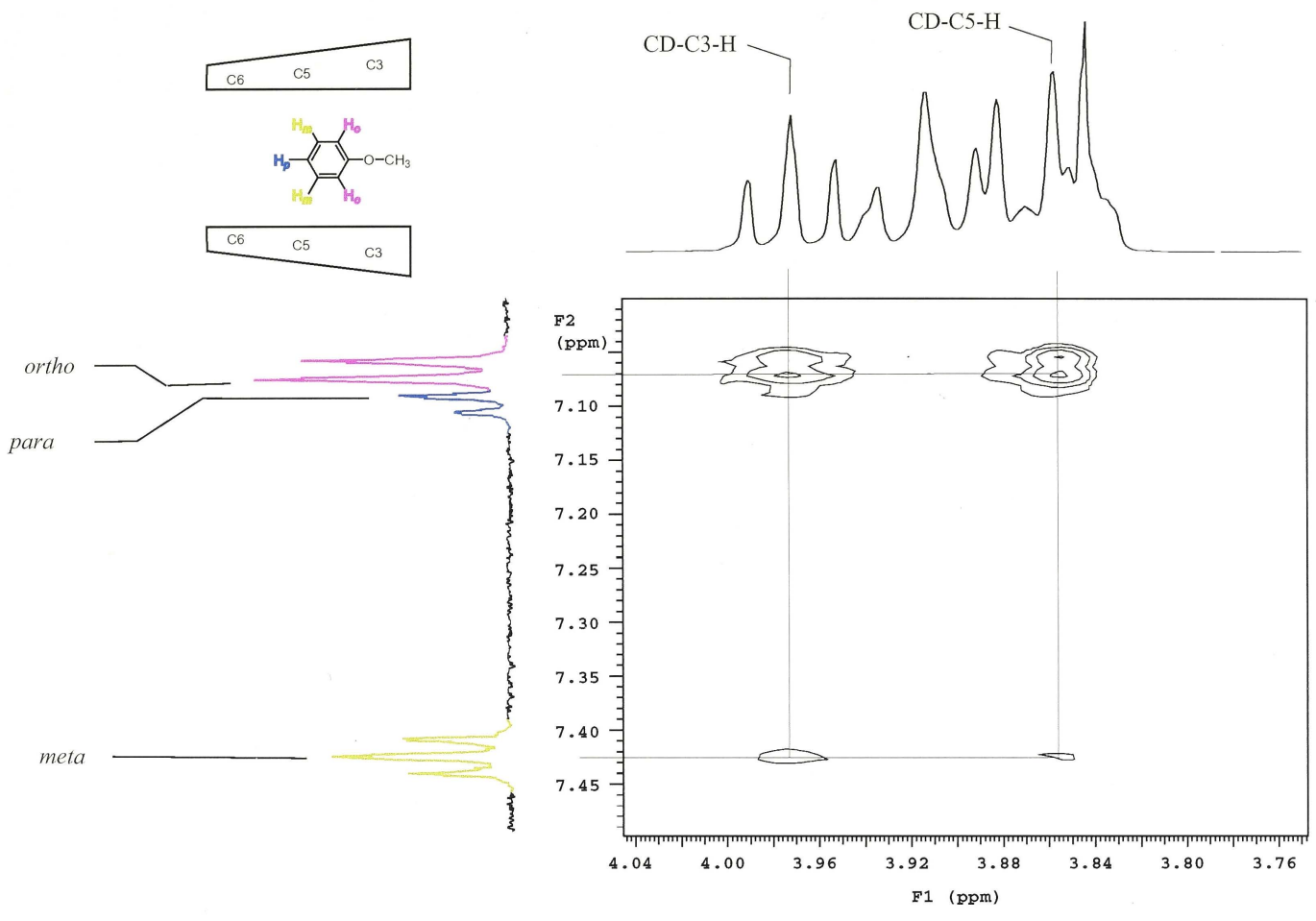


Figure 3.3 A portion of the ROESY spectrum (500 MHz) recorded of a solution of anisole **(45)** (2 mM) and b-cyclodextrin (2 mM) in D_2O, showing interactions between resonances of the cyclodextrin (x-axis) and those of the anisole **(45)** (y-axis).

Conclusion

The work described in this thesis demonstrates improved methods for carrying out aromatic chlorinations and brominations.

Rapid aromatic chlorination of a number of aromatic amides and amines has been shown to occur in a non-polar solvent in the absence of added catalyst *via* the formation of intermediate species, which provide a more electrophilic source of chlorine and participate in an intramolecular rearrangement. For phenylalkylamines the intermediates are *N*-chloroamines. Chlorination of phenylalkylamines occurs via the formation of *O*-chloroimidates; although *N*-chloroamides are able to form they have been discounted as the species responsible for the rapid aromatic chlorination. The use of the highly labile *O*-chloroimidate intermediates was extended to chlorinating co-reactants in the one pot. The rate of aromatic chlorination of simple alkylbenzenes such as *t*-butylbenzene was increased by more than one order of magnitude by adding stoichiometric amounts of amide. This demonstrated that the *O*-chloroimidates may react in both an inter- and intramolecular manner and elaborated on how these intermediates could be utilised. These reactions offer the potential to carry out aromatic chlorination under mild and selective conditions with low concentrations of chlorine. Furthermore, the use of industrial acceptable solvents such as trifluorotoluene makes these processes attractive for scale up.

Selective aromatic bromination was observed for a range of aromatic compounds in water. Both α- and β- cyclodextrin affect the regioselectivity of bromination of anisole, acetanilide and their methylated analogues, to increase the yields of specific isomers. A corollary of this is that the reactions are further improved by the substantial reduction in the yields of by-products. Since the brominations occur readily in water at ambient

temperature, and they require only stoichiometric quantities of reagents, the cyclodextrins make them very efficient chemical transformations.

Chapter Five

Experimental

5.1 General

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova 500 spectrometer. 300 MHz ^{1}H NMR spectra were recorded using a Varian Gemini 300 spectrometer. The δ values are given in parts per million (ppm) and *J*-values are given in Hz. Spectra were recorded in chloroform-*d* and referenced against tetramethylsilane δ=0 ppm unless otherwise stated. ^{1}H NMR spectra recorded in acetic acid-d_4 (δ=2.03 ppm), methanol-d_4 (δ=3.30 ppm), acetone-d_6 (δ=2.04 ppm) and dimethyl sulfoxide (DMSO)-d_6 (δ=2.49 ppm) were all referenced against residual solvent. ^{1}H NMR spectra recorded in trifluorotoluene were referenced externally with a coaxial capillary tube containing acetic acid-d_4 δ=2.69 ppm, as a secondary reference standardised against TMS in trifluorotoluene using a correction factor for the differences in bulk susceptibility arising from coaxial capillary tubes.[149] Chloroform-*d*, acetic acid-d_4, methanol-d_4, acetone-d_6 and dimethyl sulfoxide (DMSO)-d_6 were purchased from Cambridge Isotope Laboratories Inc., MA. When deuterium oxide was used as a solvent, 3-(trimethylsilyl)-3,3,2,2-tetradeuteropropionic acid sodium salt (TSPA-d_4) was used as an external standard. The following abbreviations have been used: s singlet, d doublet, t triplet, q quartet, m multiplet and b broad.

Mass spectra were recorded on the following instruments. Electron impact mass spectrometry (EI) was carried out with a Micromass VG AutoSpec M mass spectrometer. Electrospray ionisation (ESI) mass spectrometry was carried out with a Micromass VG Quattro II mass spectrometer.

High-performance liquid chromatography (HPLC) was carried out using a Waters Alliance Separation Module 2690 with a Waters 996 Photodiode array detector. A Waters Symmetry® C_{18} 3.5 μm, 4.6 x 75 mm column was used and solvent systems are specified.

Ultraviolet-visible (UV) spectra were recorded using a Shimadzu UV-2101PC UV-Vis scanning spectrophotometer at 25 °C.

Melting points (mp) were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

TLC analyses of reaction mixtures were performed on aluminium-backed plates of Kieselgel 60_{F254} silica and were visualised by using a 254 nm lamp (general) or by dipping the plates into a solution of 0.1% naphthalene-1,3-diol in 200:157:43 v/v/v ethanol-water-H_2SO_4 followed by heating with a heat gun (cyclodextrins derivatives). Column chromatography was carried out on Merck silica gel 60_{PF254}.

Water, where mentioned, was deionised and then purified with a Milli-Q^{TM} Reagent system to ensure a resistivity of < 15 MΩ cm.

α-cyclodextrin **(48)** and β-cyclodextrin **(49)** were obtained from Nihon Shokuhin Kako Co., Japan, in 99.1% purity. They were recrystallised from water and dried *in* vacuo over P_2O_5 to constant weight. All HPLC solvents were purchased from EM-Science. Reaction solvents were generally used as received. Anisole **(45)** was purchased from Sigma Chemicals and was distilled prior to usage, acetanilide **(52)** was purchased from Ajax chemicals, chlorine and hydrogen bromide were purchased from BOC gases, *t*-Butylbenzene **(16)** and 2-bromoacetanilide **(89)** were purchased from Merck, 2-bromoanisole **(86)** was purchased from Fluka, sodium hypochlorite (12.5%) was purchased from APS chemicals. Phenylethylamine **(40)** was purchased from BDH chemicals. All other chemicals were purchased from Sigma-Aldrich Chemical Company

and were used as received, except that pyridine and *N,N*-dimethylformamide was dried by storage over 4 Å molecular sieves. Ether refers to diethyl ether.

NMR tubes used for ROESY experiments were sealed with RotoTite® valves purchased from Wilmad Glass. ROESY spectra were recorded on a Varian Inova 500 spectrometer employing a mixing time of 250 ms. Samples containing α-cyclodextrin **(48)** (0.01 M) and anisole **(45)** (0.01 M), or β-cyclodextrin **(49)** (0.002 M) and anisole **(45)** (0.002 M) were degassed by *freeze-pump-thaw cycling* before use.

5.2 Experimental for Chapter 2

Stock solutions of chlorine were prepared in a partially darkened room by passing chlorine through the solvent at room temperature until the solution was bright yellow. Chlorine concentrations were determined by measuring the absorbance at 380 nm with a path length of 1 mm each time a new reaction was commenced. The calibration graph for the UV response to chlorine concentration was prepared by measuring the absorbance of a standard solution of chlorine in trifluorotoluene at 380 nm. The concentration of chlorine in the standard solution was determined by iodometric titration of iodine produced by adding potassium iodide to the chlorine solutions.[152] The result of this determination is presented in Table 2.1 and Graph 2.1 in Chapter Two.

General Procedure for the preparation of the phenylalkylamides (31), (32) and (33)

To a solution of carboxylic acid (0.02 mol) in dichloromethane (30 mL) under a N_2 atmosphere, excess thionylchloride (0.05 mol) was added slowly whilst stirring at 0 °C. Then the solution was refluxed for 1 h and then allowed to cool to room temperature and an excess of aqueous ammonia (0.10 mol) was added carefully at 0 °C to give a white precipitate. The solid was filtered off and sodium bicarbonate was added to the solution, and then extracted with dichloromethane washed with water followed by brine, then dried

with $MgSO_4$ and evaporated *in vacuo* and recrystallised from a mixture of ethanol and water.

***Phenylacetamide* (31)**

Colourless plates, 75%; m.p. 155-157 °C (Lit.[166] 155 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H, Ar), 5.66 (bs, 1H, NH), 5.43 (bs, 1H, NH), 3.60 (s, 2H, CH_2. The ^{1}H NMR spectrum of the amide **(31)** in chloroform-*d* is consistent with literature data.[166]

***3-Phenylpropionamide* (32)**

Colourless needles, 62%; m.p. 96-97 °C (Lit.[154] 97-98°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H, Ar), 5.27 (bs, 2H, NH_2), 2.98 (t, J = 7.0 Hz, 2H, β-CH_2), 2.39 (dt, J = 7.0 Hz, 2H, α-CH_2). ^{1}H NMR (acetone-d_6) δ 7.20 (m, 5H, Ar), 6.70 (bs, 1H, NH), 6.05 (bs, 1H, NH), 2.88 (t, J = 7.5 Hz, 2H, β-CH_2), 2.45 (dt, J = 7.5 Hz, 2H, α-CH_2). The ^{1}H NMR spectrum of the amide **(32)** in acetone-d_6 is consistent with literature data.[154]

***4-Phenylbutyramide* (33)**

Colourless needles, 79%; m.p. 81-83 °C (Lit.[167] 82-83°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H, Ar), 5.38 (bs, 2H, NH_2), 2.64 (t, J = 7.0 Hz, 2H, γ-CH_2), 2.22 (t, J = 7.0 Hz, 2H, α-CH_2), 1.99 (q, J = 7.0 Hz, 2H, β-CH_2). ^{1}H NMR (acetone-d_6) δ 7.23 (m, 5H, Ar), 6.70 (bs, 1H, NH), 6.05 (bs, 1H, NH), 2.62 (t, J = 7.5 Hz, 2H, γ-CH_2), 2.17 (t, J = 7.5 Hz, 2H, α-CH_2), 1.88 (q, J = 7.5 Hz, 2H, β-CH_2). The ^{1}H NMR spectrum of the amide **(33)** in acetone-d_6 is consistent with literature data.[167]

General procedure for preparation of authentic samples of the chlorinated benzene derivatives (59), (60), (61), (62), (63), (64), (67), (68) and (69)

The mono substituted aromatics were treated with chlorine in acetic acid for 24 hours and kept in the dark. Excess chlorine was removed by blowing nitrogen through the solution, then the acid solution was neutralised with sodium bicarbonate and extracted with dichloromethane, washed with water, dried with magnesium sulfate and evaporated under

reduced pressure. The products were then either characterised as a mixture or characterised as individual isomers after separation by column chromatography.

***2-t-Butylchlorobenzene* (59) *and 4-t-Butylchlorobenzene* (60)**

t-Butylbenzene **(16)** was treated with an excess of chlorine in acetic acid according to the general procedure to obtain a 20:80 isomer mixture of **(59)** and **(60)** which were separated by bulb-bulb distillation.

Ortho isomer **(59)**: Colourless liquid; bp. 135 °C/20 mmHg (Lit.[168] 130 °C/16 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 4H, Ar), 1.48 (s, 9H, *t*-Bu). ^{1}H NMR (trifluorotoluene) δ 1.40 (s, 9H, *t*-Bu). The ^{1}H NMR spectrum of the *ortho* isomer **(59)** in $CDCl_3$ is consistent with literature data.[169]

Para isomer **(60)**: Colourless liquid; bp. 95 °C/20 mmHg (Lit.[170] 209 °C/760 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 4H, Ar), 1.29 (s, 9H, *t*-Bu). ^{1}H NMR (trifluorotoluene) δ 1.17 (s, 9H, *t*-Bu). ^{1}H NMR (CCl_4) δ 7.42–7.08 (m, 4H, Ar), 1.28 (s, 9H, *t*-Bu). The ^{1}H NMR spectrum of the *para* isomer **(60)** in CCl_4 is consistent with literature data.[171]

***(2-Chlorophenyl)acetamide* (67), *(4-Chlorophenyl)acetamide* (68) and *(2,4-Dichlorophenyl)acetamide* (69)**

Phenylacetamide **(31)** was treated with an excess of chlorine in acetic acid according to the general procedure to obtain a 53:42:5 isomer mixture of **(67)**, **(68)** and **(69)** which were separated column chromatography (EtOAc:Hexane 9:1).

Ortho isomer **(67)**: Colourless crystals; mp 170-172 °C (Lit.[156] 168-172 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.21 (m, 4H, Ar), 5.40 (bs, 2H, NH_2), 3.73 (s, 2H, CH_2). ^{1}H NMR (DMSO-d_6) δ 7.60 (bs, 1H, NH), 7.46-7.35 (m, 4H, Ar), 7.08 (bs, 1H, NH), 3.66 (s,

2H, CH_2). The ^1H NMR spectrum of the *ortho* isomer **(67)** in DMSO-d_6 is consistent with literature data.[156]

Para isomer **(68)**: Colourless crystals; mp 180-182 °C (Lit.[156] 180-182 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H, Ar), 7.25 (d, J = 8.0 Hz, 2H, Ar), 5.40 (bs, 2H, NH_2), 3.56 (s, 2H, CH_2). ^1H NMR (DMSO-d_6) δ 7.60 (bs, 1H, NH), 7.46 (d, J = 8.0 Hz, 2H, Ar), 7.38 (d, J = 8.0 Hz, 2H, Ar), 7.02 (bs, 1H, NH), 3.48 (s, 2H, CH_2). The ^1H NMR spectrum of the *ortho* isomer **(68)** in DMSO-d_6 is consistent with literature data.[156]

2,4-Dichloro isomer **(69)**: Colourless crystals; mp 167-169 °C (Lit.[172] 168-169 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 4H, Ar), 5.40 (bs, 2H, NH_2), 3.69 (s, 2H, CH_2).

***3-(2-Chlorophenyl)propionamide* (63) and *3-(4-Chlorophenyl)propionamide* (64)**

Phenylpropionamide **(32)** was treated with an excess of chlorine in acetic acid according to the general procedure to obtain a 55:45 isomer mixture of **(63)** and **(64)** which were separated column chromatography (EtOAc:Hexane 3:2).

Ortho isomer **(63)**: Colourless crystals; mp 118-119 °C (Lit.[23] 119 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 4H, Ar), 5.35 (bs, 2H, NH_2), 3.10 (t, J = 7.0 Hz, 2H, β-CH_2), 2.55 (t, J = 7.0 Hz, 2H, α-CH_2). ^1H NMR (acetone-d_6) δ 7.30 (m, 4H, Ar), 6.80 (bs, 1H, NH), 6.18 (bs, 1H, NH), 3.00 (t, J = 8.0 Hz, 2H, β-CH_2), 2.49 (t, J = 8.0 Hz, 2H, α-CH_2). The ^1H NMR spectrum of the *ortho* isomer **(63)** in acetone-d_6 is consistent with literature data.[154]

Para isomer **(64)**: Colourless crystals; mp 127-129 °C (Lit.[155] 129-130 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H, Ar), 7.17 (d, J = 8.0 Hz, 2H, Ar), 5.38 (bs, 2H, NH_2), 2.95 (t, J = 8.0 Hz, 2H, β-CH_2), 2.51 (t, J = 8.0 Hz, 2H, α-CH_2).

***4-(2-Chlorophenyl)butyramide* (61) *and 4-(4-Chlorophenyl)butyramide* (62)**

Phenylbutyramide **(33)** was treated with an excess of chlorine in acetic acid according to the general procedure to obtain a 48:52 isomer mixture of **(61)** and **(62)** which were separated column chromatography (EtOAc:Hexane 1:1).

Ortho isomer **(61)**: Colourless crystals; mp 94-96 °C (Lit.[23] 96-97 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.24 (m, 4H, Ar), 5.65 (bs, 2H, NH_2), 2.80 (t, J = 7.5 Hz, 2H, γ-CH_2), 2.28 (t, J = 7.5 Hz, 2H, α-CH_2), 1.98 (apparent quintet, J = 7.5 Hz, 2H, β-CH_2). The ^{1}H NMR spectrum of the *ortho* isomer **(61)** in $CDCl_3$ is consistent with literature data.[23]

Para isomer **(62)**: Colourless crystals; mp 106-110 °C (Lit.[153] 112-113 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H, Ar), 7.10 (d, J = 8.0 Hz, 2H, Ar), 5.45 (bs, 2H, NH_2), 2.64 (t, J = 7.5 Hz, 2H, γ-CH_2), 2.22 (t, J = 8.0 Hz, 2H, α-CH_2), 1.95 (apparent quintet, J = 7.5 Hz, 2H, β-CH_2). The ^{1}H NMR spectrum of the *para* isomer **(62)** in $CDCl_3$ is consistent with literature data.[23]

Procedure for measuring rate constants for reactions of amides (31), (32), (33) and amines (40), (41), (42) with chlorine in trifluorotoluene

Approximately 2 mg of sample was dissolved 0.75 mL of trifluorotoluene containing a known amount of chlorine and stirred in the dark in a reactive-vial™. After the desired time excess chlorine and solvent were removed by blowing nitrogen over the mixture to give a solid. The solid was dissolved in $CDCl_3$ and analysed by ^{1}H NMR. The ^{1}H NMR spectra for each reaction were integrated to obtain isomer ratios (Tables 1-17 and 19-24, Appendix I. The products observed in the ^{1}H NMR were compared with authentic samples of each isomer.

Procedure for measuring rate constants for reactions of *t*-butylbenzene (16) and competition reactions (those involving *t*-butylbenzene (16) and amides (31), (32) and (33)) with chlorine in trifluorotoluene

Approximately 1 mg of *t*-butylbenzene **(16)** was dissolved in 0.3 mL of trifluorotoluene and a 0.3 mL solution of trifluorotoluene containing a known amount of chlorine was added. The ^{1}H NMR spectrum (500 MHz) was recorded initially before addition of chlorinated solution and then at regular intervals. The samples were carefully prepared to minimise exposure to light and the NMR tubes were sealed with RotoTite® valves to avoid the loss of chlorine. The deuterium lock signal was obtained from acetic acid-d_4 in a sealed capillary tube inside the NMR tube. The signal from residual acetic acid was used as a reference at 2.69 ppm. The capillary was supported with a carefully constructed Teflon spacer which was inserted and removed with a threaded extraction tool. The NMR spectra had the solvent (trifluorotoluene) electronically suppressed because (swamping of aromatic protons). The ^{1}H NMR spectra for each reaction were integrated to obtain isomer ratios (Tables 18 and 25-27, Appendix I), and the products observed in the ^{1}H NMR were compared with authentic samples of each isomer.

Competition reactions were prepared and determined in exactly the same manner as that described for *t*-butylbenzene **(16)** (above) except that amides **(31)**, **(32)** and **(33)** (1 mol. equiv.) were added to the mixture of *t*-butylbenzene **(16)** in trifluorotoluene prior to addition of chlorinated solution.

5.3 Experimental for Chapter 3

Hypochlorous acid

Prepared using a modification of the method of Breslow *et al.*[102] 500 mL of sodium hypochlorite was shaken with 2g of HgO, then the solution was carefully acidified by adding concentrated H_2SO_4 (while cooling the vessel in an ice bath) until the pH was 4.2. The solution was distilled under vacuum (20 mmHg) at 35 °C while using an ice

condenser. The volume of the distillate collected was around 60 mL which was stored in a dark bottle with 1 g of HgO present at 0 °C.

Faint yellow coloured liquid. UV spectrum (broad shoulder at λ=300 nm, λmax = 234 nm; ε =100. Lit.[173] λmax = 234 nm; ε =99.8.) Spectroscopic data is consistent with those reported.[173]

Pyridinium Dichlorobromate (55)

Prepared by using a method described by Muathen *et al.*[147] A cold mixture of HBr (33% solution in acetic acid, 24.3 g, 0.1 mol) and dichloromethane (100 mL) was placed in an addition funnel. The cold solution was added drop wise to a vigorously stirred, cold solution of pyridine (8 g, 0.1 mol) in CH_2Cl_2 (300 mL) at such a rate that the temperature does not rise above 10 °C. After the addition was complete the mixture was allowed to cool down to 0 °C. Chlorine gas was bubbled into the mixture (fume cupboard), maintaining the temperature between 0-10 °C, until complete precipitation of the complex took place. Cold carbon tetrachloride (200 mL) was added and the resultant yellow solid was filtered under suction and washed with carbon tetrachloride to give the product.

Pale yellow crystals (22 g, 95%), mp 140-142 °C. (Lit.[147] 140-142 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.5 (1H, br s, NH), 9.1 (2H, m, Ar), 8.7 (1H, m, Ar), 8.2 (2H, m, Ar). Spectroscopic data are consistent with those reported.[147]

Synthesis of 6^A-Amino-6^A-deoxy-α-cyclodextrin (α-CDNH$_2$) (84)

6^A-O-(p-Toluenesulfonyl)-α-cyclodextrin (α-CDOTs)

α-CD **(48)** (10.0 g, 0.013 mol) was dissolved in dry pyridine (800 mL) by gentle warming and shaking. The mixture was cooled to 5 °C and *p*-toluenesulfonyl chloride (9.82 g, 0.051 mol) was added in small portions and the solution was stirred at room

temperature for 75 minutes whilst monitoring the reaction by TLC. The resultant mixture was evaporated to a volume of about 150 mL and poured into ice-cold acetone 2.5 L. The fine white precipitate that formed was allowed to settle over 1 h, then most of the supernatant was decanted and the solid was collected by gravity filtration. The fine white precipitate was then washed with cold acetone (100 mL) and allowed to dry over night to give the crude product. The crude product was dissolved in water (1 L) and the solution was filtered and loaded onto a Diaion HP-20 column (310 x 25 mm). The column was eluted with a water-methanol solvent gradient. The desired product was obtained when the column was eluted with 20-30% methanol. The fractions containing the desired product were concentrated under reduced pressure and freeze-dried to give the product.

White powder (2.8 g, yield 24 %), m.p. 161 °C (decomposed) (Lit.[174] 159-162 °C) (decomposed)]. ^{1}H NMR (300 MHz, D_2O) δ 7.74 (2H, d, *J*=7.5, ArH), 7.42 (2H, d, *J*=7.5, Ar), 4.93-3.34 (42H, m, CD), 2.35 (3H, s, CH_3). Mass spectrum (ESI) *m/z* (%) 1150 ($M+Na^+$). Spectroscopic data are consistent with those reported.[175]

6^A-Azido-6^A-deoxy-α-cyclodextrin (α-CDN$_3$)

α-CDOTs (2.1×10^{-3} mol) was suspended in 25 mL of water and the solution was heated to 80 C. To the stirring hot solution, sodium azide (1.50 g 0.023 mol) was added and the mixture stirred for 5 hours, then it was cooled to room temperature and poured onto acetone (150 mL). The fine white precipitate was collected by filtration and dried to yield the crude product. The crude product was recrystallised from water and freeze-dried to yield the title compound.

Colourless powder (1.0 g, yield 70%), m.p. 218 °C (dec.) [Lit.[175] 217 °C (dec)]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.7-3.2 (59H, m, CD). Mass spectrum (ESI) *m/z* (%) 997 ($M+H^+$). Spectroscopic data are consistent with those reported.[175]

***6^A-Amino-6^A-deoxy-α-cyclodextrin (α-CDNH$_2$)* (84)**

α-CDN_3 (0.5 g, 0.5 mmol) and triphenylphosphine (0.25 g, 0.095 mmol) were dissolved in DMF (10 mL). Ammonia solution (2 mL, approx. 25%) was added to the mixture

which was stirred for 4 hours at room temperature. Then the mixture was poured onto acetone (50 mL) and the resultant precipitate was collected by filtration to yield the crude product. The crude product was dissolved in water (100 mL) and Bio-Rex 70 (3 g, H^+ form) was added. The mixture was stirred overnight. The resin was collected using a sintered glass funnel and rinsed with water (4 x 25 mL). The product was obtained by elution of the resin with 0.5 M ammonia solution 300 (mL). The fractions containing the desired product were concentrated under reduced pressure and freeze-dried to give the amino cyclodextrin derivative.

Colourless powder (245 mg, yield 48%), m.p. 200 °C (dec) [Lit.[174] 200 °C (dec)]. (^{1}H NMR (300 MHz, D_2O) δ 5.9-3.2 (42H, m, CD). Mass spectrum (ESI) *m/z* (%) 996 ($M+Na^+$). Spectroscopic data are consistent with those reported.[175]

Synthesis of 6^A-Amino-6^A-deoxy-β-cyclodextrin (β-CDNH$_2$) (85)

1-(p-Toluenesulfonyl)imidazole

p-Toluenesulfonyl chloride (80 g, 0.42 mol) in 250 mL of dry dichloromethane was added drop wise over 90 minutes to a solution of imidazole (65 g, 0.95 mol) in 250 mL of dry dichloromethane at 0 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature and then stirred vigorously for 2 hours. The reaction was filtered through a pad of silica gel (100 g), which was washed with 500 mL of 1:1 ethyl acetate-hexane. The filtrate was concentrated under reduced pressure, leaving a residue to which is added 50 mL of ethyl acetate then 500 mL of hexane. The suspension was filtered to give the product.

White solid (81 g yield 88 %), m.p. 78-79 °C (Lit.[176] 77.0-78.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, s, Im), 7.83 (2H, d, *J*=8.0, Ar), 7.34 (2H, d, *J*=8.0, Ar), 7.30 (1H, s, Im), 7.08 (1H, s, Im), 2.43 (3H, s, CH_3). Spectroscopic data are consistent with those reported.

6^A-O-(p-Toluenesulfonyl)-β-cyclodextrin (β-CDOTs)

β-CD **(49)** (40.0 g, 0.035 mol) was dissolved in water (900 mL) by heating to 60 °C with vigorous stirring. The mixture was allowed to cool to room temperature and finely powdered 1-(*p*-toluenesulfonyl)imidazole (31.3 g, 0.141 mol) was added in one portion and the solution was stirred at room temperature for 2 hours whilst under a nitrogen atmosphere. Sodium hydroxide (18 g, 0.45 mol) in 50 mL of water was added over 20 minutes to the reaction mixture and this allowed to stir for a further 10 minutes. Unreacted 1-(*p*-toluenesulfonyl)imidazole was separated by filtration through a sintered glass funnel and the reaction was quenched by adding (48.2 g, 0.90 mol) of ammonium chloride. The mixture was concentrated to half its original volume by blowing a stream of air on the surface overnight. The resulting suspension was filtered through a large sintered glass funnel and the collected solid was washed with two 100 mL portions of ice water and one 200 mL portion of cold acetone, then freeze-dried to give the product.

Colourless powder (17.5 g, yield 38%), m.p. >250 °C (decomposed). ^{1}H NMR (300 MHz, D_2O) δ 7.73 (2H, d, *J*=9.0, Ar), 7.53 (2H, d, *J*=9.0, Ar), 5.05 (7H, m, CD-H_1) 4.00-3.50 (42H, m, CD-H), 2.57 (3H, s, Ar-CH_3). Mass spectrum (ESI) *m/z* (%) 1311 ($M+Na^+$). Spectroscopic data are consistent with those reported.[175]

6^A-Azido-6^A-deoxy-β-cyclodextrin (β-CDN$_3$)

The azido derivative was made in exactly the same way described for the 6^A-Azido-6^A-deoxy-α-cyclodextrin (α-CDN_3) except that β-CDOTs was used instead of α-CDOTs.

Colourless powder (yield 65%), m.p. >250 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.9-3.2 (69H, m, CD). Mass spectrum (ESI) *m/z* (%) 1160 ($M+Na^+$). Spectroscopic data are consistent with those reported.[175]

***6^A-Amino-6^A-deoxy-β-cyclodextrin (β-CDNH$_2$)* (85)**

The title compound was made in exactly the same way described for 6^A-Amino-6^A-deoxy-α-cyclodextrin (α-$CDNH_2$) **(84)** except that β-CDN_3 was used instead of α-CDN_3.

Colourless powder (yield 55%), m.p. >250 °C (dec). ^{1}H NMR (300 MHz, D_2O) δ 5.00 (7H, br s, CD-H_1), 4.0-3.8 (28H, m, CD), 3.7-3.4 (14H, m, CD). Mass spectrum (ESI) *m/z* (%) 1134 ($M+H^+$). Spectroscopic data are consistent with those reported.[175]

3-Methylacetanilide (58)

3-methyltoluidine was acetylated using standard literature method.[177] Where 3-Methyltoluidine (1.0 g, 6.05 x 10^{-3} mol) was dissolved in excess acetic anhydride (25 mL 50 eq), then triethylamine (0.61 g, 6.05 x 10^{-3} mol) was added and the mixture was stirred under reflux for 6 h. Then water was added and the solution was extracted with ethyl acetate. The extracts were washed with 3 x water and 3 x 10% HCl. The organic layer was dried with $MgSO_4$ and evaporated *in vacuo* then recrystallised from a mixture of chloroform and ether to give 3-Methylacetanilide **(58)**.

Colourless crystals (2.07 g, 74%), m.p. 64-66 °C (Lit.[172] 66 °C). ^{1}H NMR (300 MHz, CD_3OD) δ 7.35 (s, 1H, Ar-H2), 7.31 (d, J = 7.5, 1H, Ar-H6), 7.15 (t, J = 7.8, 1H, Ar-H5), 6.90 (d, J = 7.5, 1H, Ar-H4), 2.30 (s, 3H, CH_3), 2.10 (s, 3H, $C(O)CH_3$).

General Procedure for the preparation of the 3-methylanisole bromides (95), (96) and (97)[178]

3-Methylanisole **(57)** (10 g, mol) was added drop wise to a stirring solution of bromine (30 g, mol) in glacial acetic acid (13.5 mL) with the temperature being kept below 10 °C. After the addition of bromine was complete (approx. 30 minutes) the reaction was stirred for a further 60 minutes. The white crystals of crude 4,6-dibromo-3-methylanisole **(95)** were filtered off and recrystallised from ethanol. The filtrate containing bromine was quenched with excess sodium bisulfite, neutralised with sodium bicarbonate and extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed with water, dried with $MgSO_4$ and evaporated *in vacuo* to give a 5:3:5:1 crude mixture of **(95)**, **(96)**, **(94)** and **(97)** as a slightly yellow coloured oil. The characteristic resonances for compounds **(95)**, **(96)**, **(94)** and **(97)** are shown in Table 3.8.

4,6-dibromo-3-methylanisole (95)

Colourless needles (4.3 g, 74%), m.p. 74-76 °C (Lit.[179] 76 °C). ^{1}H NMR (300 MHz, CD_3OD) δ 7.60 (s, 1H, Ar-H6), 6.69 (s, 1H, Ar-H3), 3.84 (s, 3H, $C(O)CH_3$), 2.33 (s, 3H, CH_3).

Chlorination of Anisole in water

Anisole (10.8 mg, 0.1 mmol) was dissolved in 1.5 mL of methanol and added to a 250 mL RB flask, to which cyclodextrin (1.0 mmol, 10 eq) and 100 mL of milli Q water were added and the solution was stirred vigorously. Hypochlorous acid (1.0 mmol, 10 eq) was added and the total volume was made up with milli Q water to 150 mL. The solution was stirred at room temperature for 1 h. After the desired time, the reaction was quenched by adding an excess of $NaHSO_3$, then extracted with 2 x 80 mL ether. The ether extracts were washed with water 100 mL, dried with $MgSO_4$ and evaporated *in vacuo* to give a brown coloured liquid. Analysis of the mixture using ^{1}H NMR spectroscopy showed the presence of starting material **(45)**, *o*-chloroanisole **(46)**, *p*-chloroanisole **(47)** and 2,4-dichloroanisole **(77)**. The ratios of components present are shown in table 3.1. These were determined through integration of key resonances (Table 3.6), which were assigned based on comparison with the spectra of authentic samples.

Chlorination of Anisole in the presence of *n*-Octanol in water

Anisole (0.0108 g, 0.1 mmol) was dissolved in 1.5 mL of methanol and added to a 250 mL RB flask, to which cyclodextrin (1.0 mmol, 10 eq), *n*-octanol (1.0 mmol, 10 eq) and 100 mL of milli Q water were added and the solution was stirred vigorously. Hypochlorous acid (1.0 mmol, 10 eq) was added and the total volume was made up with milli Q water to 150 mL. The solution was stirred at room temperature for 1 h. After the desired time, the reaction was quenched by adding an excess of $NaHSO_3$, and then extracted with 2 x 80 mL ether. The ether extracts were washed with water 100 mL, dried with $MgSO_4$ and evaporated *in vacuo* to give a brown coloured liquid. The mixture was

analysed in the same way as that described for the previous experiment, with the ratio of products shown in Table 3.2.

General Bromination procedure

Aromatic substrate (2.0×10^{-4} mol) in methanol (1.5 mL, 1% v/v) was added to cyclodextrin (2.0×10^{-3} mol) in water (100 mL) and the resulting solution stirred vigorously. Pyridinium dichlorobromate **(55)** (2.2×10^{-4} mol) was added and the total volume made up to 150 mL with water. The resulting solution was stirred at room temperature for 1 h (except for reaction of **(56)**, which was stirred for 24 h), and then the reaction quenched by the addition of an excess of $NaHSO_3$.The reaction mixture was extracted with ether (2×80 mL), and the ether extracts washed with water (100 mL), dried and evaporated *in vacuo*. The residue was analysed by integration of key resonances in the ^1H NMR spectrum (Tables 3.6 and 3.7) recorded in $CDCl_3$, CD_3OD or d_6-DMSO depending on solubility, to determine the ratios of the components (shown in Tables 3.3, 3.4, 3.5, 3.8 and 3.9).

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Appendix I – Tables of Raw Data Used for Determining Rate Constants

Table 1 Data for the reaction of *t*-butylbenzene **(16)** and chlorine (0.05 M) in trifluorotoluene at 25 °C (Graph 2.3)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	99.5	0	0.5	0.995	-0.005
172800	99.0	>0.0	1.0	0.990	-0.011
360000	97.5	0.5	2.0	0.975	-0.025
604800	95.0	1.0	4.0	0.950	-0.048

Table 2 Data for the reaction of *t*-butylbenzene **(16)** and chlorine (0.10 M) in trifluorotoluene at 25 °C (Graph 2.3)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	99.0	>0.0	1.0	0.990	-0.008
172800	98.0	0.5	1.5	0.980	-0.020
345600	95.5	1.0	3.5	0.955	-0.045
518400	93.0	1.5	5.5	0.930	-0.071

Table 3 Data for the reaction of *t*-butylbenzene **(16)** and chlorine (0.20 M) in trifluorotoluene at 25 °C (Graph 2.3)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	98.5	<0.5	1.0	0.985	-0.016
172800	96.0	0.5	3.5	0.960	-0.040
345600	92.5	1.5	6.0	0.925	-0.078

Table 4 Data for the reaction of *t*-butylbenzene **(16)** and chlorine (0.90 M) in trifluorotoluene at 25 °C (Graph 2.3)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	92.5	1.5	6.0	0.925	-0.079
172800	82.0	3.0	15.0	0.820	-0.197
259200	74.0	4.5	21.5	0.740	-0.301
360000	66.5	5.5	28.5	0.665	-0.406

Table 5 Data for the reaction of phenylbutyramide**(33)** and chlorine (0.01 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	95.5	2.5	2.0	0.955	-0.048
1800	89.0	5.5	4.5	0.890	-0.115
3600	76.0	13.0	11.0	0.760	-0.273
7200	57.0	23.5	19.5	0.570	-0.564

Table 6 Data for the reaction of phenylbutyramide**(33)** and chlorine (0.02 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	71.0	16.0	13.0	0.710	-0.342
1800	42.5	31.5	26.0	0.425	-0.860
3600	15.5	46.5	38.0	0.155	-1.851
7200	3.0	53.5	43.5	0.030	-3.540

Table 7 Data for the reaction of phenylbutyramide**(33)** and chlorine (0.10 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	26.5	40.5	33.0	0.265	-1.332
1800	5.5	52.0	42.5	0.055	-2.882
3600	0.0	55.0	45.0	0.000	-
7200	0.0	55.0	45.0	0.000	-

Table 8 Data for the reaction of phenylbutyramide**(33)** and chlorine (0.20 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	17.0	45.5	37.5	0.170	-1.772
1800	2.0	54.0	44.0	0.020	-3.963
3600	0.0	55.0	45.0	0.000	-
7200	0.0	55.0	45.0	0.000	-

Table 9 Data for the reaction of phenylbutyramide**(33)** and chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	12.5	48.0	39.5	0.125	-2.087
1800	1.0	54.5	44.5	0.010	-4.605
3600	0.0	55.0	45.0	0.000	-
7200	0.0	55.0	45.0	0.000	-

Table 10 Data for the reaction of phenylbutyramide**(33)** and chlorine (1.01 M) in trifluorotoluene at 25 °C (Graph 2.5)

time (s)	starting material **(33)** %	*ortho* isomer **(61)** %	*para* isomer **(62)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	9.5	50.0	40.5	0.095	-2.343
1800	0.0	55.0	45.0	0.000	-
3600	0.0	55.0	45.0	0.000	-
7200	0.0	55.0	45.0	0.000	-

Table 11 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.01 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	100.0	0	0	1.000	0
1800	99.0	0.5	0.5	0.990	-0.007
3600	98.0	1.0	1.0	0.980	-0.019
7200	95.5	2.5	2.0	0.955	-0.048

Table 12 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.02 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	87.0	7.0	6.0	0.870	-0.139
1800	65.5	19.0	15.5	0.655	-0.420
3600	46.5	29.5	24.0	0.465	-0.768
7200	22.5	42.5	35.0	0.225	-1.500

Table 13 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.05 M) in trifluorotoluene at 25 °C (Graphs 2.6 and 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	80.0	11.0	9.0	0.800	-0.219
1800	53.5	25.5	21.0	0.535	-0.623
3600	21.0	43.5	35.5	0.210	-1.560
7200	4.5	52.5	43.0	0.045	-3.058

Table 14 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.10 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	62.0	21.0	17.0	0.620	-0.476
1800	31.5	37.5	31.0	0.315	-1.155
3600	8.0	50.5	41.5	0.080	-2.488
7200	1.0	54.5	44.5	0.010	-4.605

Table 15 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.20 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	59.0	22.5	18.5	0.590	-0.531
1800	30.5	38.5	31.0	0.305	-1.194
3600	8.0	50.5	41.5	0.080	-2.563
7200	0.0	55.0	45.0	0.000	-

Table 16 Data for the reaction of phenylpropionamide **(32)** and chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0.0	0	1.000	0
900	49.0	28.0	23.0	0.490	-0.713
1800	24.0	42.0	34.0	0.240	-1.418
3600	4.5	52.5	43.0	0.045	-3.057
7200	0.0	54.5	45.5	0	-

Table 17 Data for the reaction of phenylpropionamide **(32)** and chlorine (1.01 M) in trifluorotoluene at 25 °C (Graph 2.7)

time (s)	starting material **(32)** %	*ortho* isomer **(63)** %	*para* isomer **(64)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1.000	0
900	48.5	28.5	23.0	0.490	-0.713
1800	21.5	43.0	35.5	0.215	-1.537
3600	4.5	52.5	43.0	0.045	-3.146
7200	0.0	55.0	45.0	0	-

Table 18 Data for the treatment of *O*-chloro-3-phenylpropionamide **(65)** with chlorine (variable concentrations) in trifluorotoluene at 25 °C (Graph 2.8)

Chlorine concentration (M)	% *N*-chloroamide **(66)**	% amide **(65)**
0.005	0.0	100
0.01	1.0	99.0
0.02	7.0	93.0
0.05	28.5	71.5
0.10	53.0	47.0
0.20	70.5	29.5
0.50	98.0	2.0
0.90	100	0

Table 19 Data for the reaction of phenylacetamide **(31)** and chlorine (0.02 M) in trifluorotoluene at 25 °C (Graph 2.10)

time (s)	starting material **(31)** %	*ortho* isomer **(67)** %	*para* isomer **(68)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0.0	0.0	1.000	0
86400	100.0	0.0	0.0	1.000	0
172800	99.0	0.5	0.5	0.990	-0.010
345600	97.5	1.5	1.0	0.975	-0.025
532800	96.0	2.5	1.5	0.960	-0.041

Table 20 Data for the reaction of phenylacetamide **(31)** and chlorine (0.05 M) in trifluorotoluene at 25 °C (Graph 2.9 and 2.10)

time (s)	starting material **(31)** %	*ortho* isomer **(67)** %	*para* isomer **(68)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0.0	0.0	1.000	0
86400	94.5	3.5	2.0	0.945	-0.056
172800	86.5	9.0	4.5	0.865	-0.145
345600	78.5	14.0	7.5	0.785	-0.240
540000	66.0	22.0	12.0	0.660	-0.410

Table 21 Data for the reaction of phenylacetamide **(31)** and chlorine (0.10 M) in trifluorotoluene at 25 °C (Graph 2.10)

time (s)	starting material **(31)** %	*ortho* isomer **(67)** %	*para* isomer **(68)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0.0	0.0	1.000	0
86400	88.5	7.5	4.0	0.885	-0.121
172800	70.0	19.5	10.5	0.700	-0.353
360000	48.5	33.5	18.0	0.485	-0.723
532800	37.5	40.5	22.0	0.375	-0.980

Table 22 Data for the reaction of phenylacetamide **(31)** and chlorine (0.20 M) in trifluorotoluene at 25 °C (Graph 2.10)

time (s)	starting material **(31)** %	*ortho* isomer **(67)** %	*para* isomer **(68)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0.0	0.0	1.000	0
86400	81.0	12.5	6.5	0.810	-0.213
172800	56.0	28.5	15.5	0.560	-0.583
345600	37.0	41.0	22.0	0.370	-0.986
532800	20.5	51.5	28.0	0.205	-1.584

Table 23 Data for the reaction of phenylacetamide **(31)** and chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.10)

time (s)	starting material **(31)**	*ortho* isomer **(67)**	*para* isomer **(68)**	2,4-dichloro isomer **(69)**	$[A]/[A]_o$	$\ln([A]/[A]_o)$
	%	%	%			
0	100.0	0.0	0.0	0	1.000	0
86400	78.5	14.0	7.5	0	0.785	-0.240
172800	60.5	25.5	14.0	0	0.605	-0.502
360000	30.0	45.5	24.0	0.5	0.300	-1.200
532800	14.0	55.0	28.5	2.5	0.140	-1.966

Table 24 Data for the reaction of phenylacetamide **(31)** and chlorine (0.96 M) in trifluorotoluene at 25 °C (Graph 2.10)

time (s)	starting material **(31)**	*ortho* isomer **(67)**	*para* isomer **(68)**	2,4-dichloro isomer **(69)**	$[A]/[A]_o$	$\ln([A]/[A]_o)$
	%	%	%			
0	100.0	0.0	0.0	0	1.000	0
86400	75.0	16.0	9.0	0	0.750	-0.285
174600	52.0	31.0	16.5	0.5	0.520	-0.652
345600	25.0	47.5	24.5	3.0	0.250	-1.386
532800	13.5	53.0	26.5	7.0	0.135	-1.995

Table 25 Data for competition reactions between *t*-butylbenzene **(16)** and phenylacetamide **(31)** with chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.12)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	85.5	3.0	11.5	0.855	-0.157
172800	77.5	4.5	18.0	0.775	-0.254
259200	70.0	6.0	24.0	0.700	-0.357
345600	59.0	8.0	33.0	0.590	-0.524

Table 26 Data for competition reactions between *t*-butylbenzene **(16)** and phenylpropionamide **(32)** with chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.12)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	68.0	6.5	25.5	0.680	-0.383
172800	49.0	10.0	41.0	0.490	-0.710
259200	32.0	13.5	54.5	0.320	-1.140
345600	20.0	16.0	64.0	0.200	-1.620

Table 27 Data for competition reactions between *t*-butylbenzene **(16)** and phenylbutyramide **(33)** with chlorine (0.50 M) in trifluorotoluene at 25 °C (Graph 2.12)

time (s)	starting material **(16)** %	*ortho* isomer **(59)** %	*para* isomer **(60)** %	$[A]/[A]_o$	$\ln([A]/[A]_o)$
0	100.0	0	0	1	0
86400	56.5	8.5	35.0	0.565	-0.567
172800	35.5	13.0	51.5	0.355	-1.040
259200	16.0	17.0	67.0	0.160	-1.850
345600	8.5	18.0	73.5	0.085	-2.470

Table 28 UV-visible absorbance data for reaction of hypochlorous acid with β-amino cyclodextrins at 25 °C.

Concentration of HOCl (M)	Concentration of amino-cyclodextrin (M)	Ratio of HOCl:Amine	Absorbance at 234 nm
6.526×10^{-3}	0	-	0.523
3.263×10^{-3}	6.526×10^{-3}	0.5:1	0.015
6.526×10^{-3}	6.526×10^{-3}	1:1	0.021
1.305×10^{-2}	6.526×10^{-3}	2:1	0.518
1.958×10^{-2}	6.526×10^{-3}	3:1	1.070
6.526×10^{-3}	3.263×10^{-3}	1:0.5	0.495
6.526×10^{-3}	1.305×10^{-2}	1:2	0.012
6.526×10^{-3}	1.958×10^{-2}	1:3	0.010

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Aust. J. Chem., 2003, **56**, 000–000

0004-9425

Manuscript accepted for publication

Effect of Cyclodextrins on Electrophilic Aromatic Bromination in Aqueous Solution

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Dedicated to Professor John H. Bowie with best wishes on the occasion of his 65th birthday.

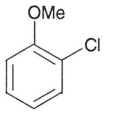
Abstract – Cyclodextrins act as molecular reactors to change the ratios of the products of reactions of anisole, acetanilide, 3-methylanisole and 3-methylacetanilide with pyridinium dichlorobromate. With anisole and acetanilide, bromination at the *para* position is favoured over *ortho* substitution, and the effect is greatest with α-cyclodextrin. In the reactions of the methylanisole and methylacetanilide, the cyclodextrins afford higher yields of monobrominated products and less of the di- and tribromides, and β-cyclodextrin has the most effect. These outcomes can be attributed to inclusion of the substrates within the cyclodextrins restricting access of the reagent adjacent to the methoxy and acetamido groups. The yields of 4-bromoanisole, 4-bromoacetanilide, 4-bromo-3-methylanisole and 4-bromo-3-methylacetanilide are thus increased from 73 to 94, 55 to 98, 37 to 86, and 39 to 72%, respectively. Perhaps more significantly, the quantities of the corresponding by-products are substantially reduced, from 27 to 6, 45 to 2, 63 to 14, and 61 to 28%. Since the reactions occur readily in water at ambient temperature, the cyclodextrins make them very efficient.

Introduction

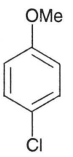
Cyclodextrins have attracted considerable attention as enzyme mimics, due to their ability to form inclusion complexes with small organic compounds in water and catalyse reactions of the included species.[1–5] They have also been exploited as molecular reactors, where they control the assembly of reactants to change the outcomes of chemical transformations.[6–16] Examples of the latter include the covalent attachment of dipolarophiles to cyclodextrins to reverse the regioselectivity of cycloadditions with nitrile oxides[6,7] and the development of a urea-linked cyclodextrin dimer to bias competing reactions to give indigoid dyes.[8]

Probably the most straightforward examples of cyclodextrin molecular reactors are those that involve a change in the regioselectivity of reaction as a result of a substrate being included in such a way as to restrict access of a reagent. Pioneering research in this area by Breslow *et al.*[9–11] showed that cyclodextrins alter the regioselectivity of aromatic substitution. Hypochlorous acid chlorination of anisole (3a) in the absence of a cyclodextrin gave the chlorides (1) and (2), in the ratio of *ca.* 2 : 3. When the reactions were repeated in the presence of either α- or β-cyclodextrin, substantially more of the *para* isomer (2) was formed, particularly in the former case. Breslow *et al.*[9–11] reasoned that, in the inclusion complexes with the cyclodextrins, the *ortho* positions of the anisole (3a) are shielded from chlorination while the *para* position is still accessible. With this system it was suggested that the chlorination involves cyclodextrin hypochlorites but a related study of selective *para* chlorination of acetanilide (3b) in the presence of cyclodextrins[12] discounted the involvement of such intermediates. The reactions discussed above were carried out in water, which has the added advantage of being an

environmentally benign solvent. The cyclodextrins facilitate the use of this medium by increasing the solubility of organic substrates.



(1)



(2)

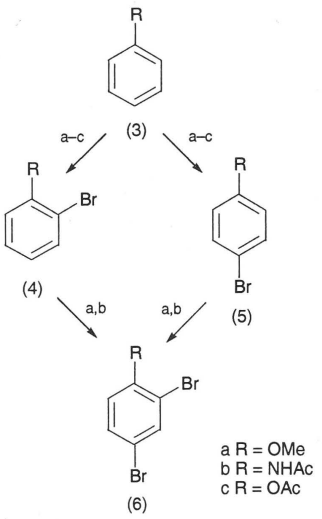
Another example of the use of cyclodextrins to influence aromatic substitution was reported by Komiyama and Hirai,[13,14] where the regioselectivity of the Reimer-Tiemann reaction of phenol with chloroform was altered, again in favour of *para* substitution. Tee and Bennett[17] investigated the effects of cyclodextrins on the bromination of anisole (3a) with bromine/KBr in water, but in that system the oligosaccharides did not alter the regioselectivity. Instead, they retarded the reaction rate, due to inclusion of both the substrate and the brominating agent. In light of the lack of regiocontrol in this system, the recent account of the use of pyridinium dichlorobromate for aromatic bromination in aqueous ethanol[18] prompted us to investigate the effect of employing cyclodextrins with this reagent. As reactants for the study, we chose anisole (3a) and acetanilide (3b), in order to make direct comparisons with the chlorination of those compounds. Phenyl acetate (3c), and the methyl-substituted anisole (7a) and acetanilide (7b) were also selected as substrates, on the basis that the ester (3c) is less reactive, and the ether (7a) and amide (7b) more reactive, towards aromatic substitution.

Results and Discussion

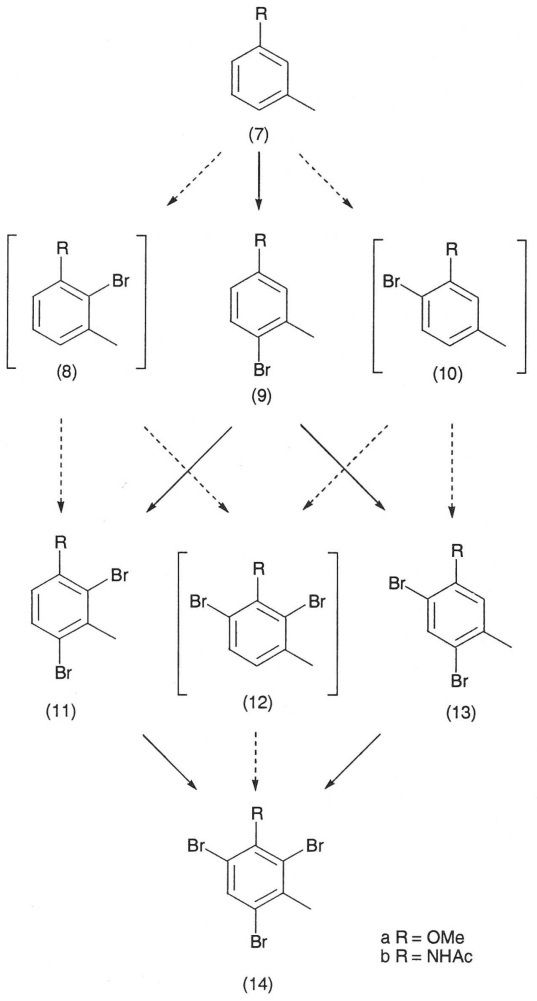
Each of the substrates (3a–c) and (7a,b) (1.3 mM) was treated with pyridinium dichlorobromate (0.6, 1.1 and/or 2.2 mol. equiv.), in water containing methanol (1%, v/v). The reactions were carried out at room temperature, for either 1 or 16 h, in the absence of a cyclodextrin and in the presence of either α- or β-cyclodextrin (10 mol. equiv.). After work-up, the crude product mixtures were analysed using ^{1}H NMR spectroscopy. The ratios of the components present are shown in Table 1. These were determined through integration of key resonances (Table 2), that were assigned based on comparison with the spectra of authentic samples in the cases of compounds (3a–c), (4a), (5a,b), (7a,b), (11a), (13a) and (14a), and on data from the literature[19–25] for the bromides (4b,c), (5c), (6a,b) and (9a,b). Resonances were assigned to the methylacetanilides (11b), 13b) and (14b) by analogy with the spectra of the corresponding methylanisoles (11a), (13a) and (14a), and by comparison of observed chemical shifts and coupling constants with calculated values.[26] An unidentified compound (X) was also observed in reactions of the methylacetanilide (7b). It seems likely that this is the product of a secondary process, since it was not seen during the initial stages of reaction.

The reactions of anisole (3a) and acetanilide (3b) with 1.1 equiv. of the brominating agent gave small amounts of the dibromides (6a) and (6b), respectively, presumably *via* the corresponding monobromides (4a,b) and (5a,b) (Scheme 1). Phenyl acetate (3c) reacted to a much lesser extent, even after a much longer reaction time, and only the monobromides (4c) and (5c) were produced, i.e. there was no evidence of formation of the dibromide (6c). In the reactions of the methylanisole (7a) and methylacetanilide (7b), unreacted starting materials and the corresponding monobromides (9a,b), dibromides

(11a,b) and (13a,b), and tribromides (14a,b), and the unidentified product (X) in the case of the acetanilide (7b), accounted for at least 95 mol% of the product mixtures. This was determined by analysis of ^{1}H NMR spectra and particularly through comparison of the integrations of all the methyl proton resonances relative to those of the aromatic protons. While it is conceivable that the monobromides (8a,b) and (10a,b), and the dibromides (12a,b) could also have been produced (Scheme 2), they were each detected at most in only trace quantities (≤3%).



Scheme 1



Scheme 2

In the reactions carried out in the absence of a cyclodextrin, the formation of only small amounts of the dibromides (6a,b) from anisole (3a) and acetanilide (3b), respectively, relative to the yields of the corresponding monobromides (4a,b) and (5a,b) (Table 1, entries 1 and 4), indicates that the bromo substituents of (4a,b) and (5a,b) reduce the reactivity of these systems towards further aromatic substitution. This deactivation is typical of halogens and is greatest with the acetanilides (3b)–(5b). By contrast, the yields

of the dibromides (11a,b) and (13a,b) from the methylanisole (7a) and methylacetanilide (7b) are more substantial (Table 1, entries 10, 13, 16, 17 and 20), particularly with the anisole (7a), where monobromination appears to activate the system to further reaction. Presumably, the combination of methoxy and methyl substituents perturbs the balance of resonance and inductive effects normally seen with a bromo group. Significant quantities of (8a,b), (10a,b) and (12a,b) do not build up in the reactions of (7a,b). This is probably due largely to the selectivity of bromination *para* to a methoxy or acetamido group, but another contributing factor may be that, like (9a,b), the bromides (8a,b), (10a,b) and (12a,b) are unusually reactive, and once formed react further to give (11a,b), (13a,b) and (14a,b), respectively.

In the reactions of anisole (3a) and acetanilide (3b), both α- and β-cyclodextrin change the ratios of formation of the monobrominated products (4a,b) and (5a,b) in favour of the *para*-substituted isomers (5a,b) (Table 1, entries 1–6). The effect is greatest with α-cyclodextrin. It is thus apparent that the cyclodextrins limit *ortho* bromination of the substrates (3a,b), presumably through the formation of inclusion complexes restricting access of the brominating agent, in a manner that is directly analogous to the effect of cyclodextrins on chlorination reported previously.[9–12] In the case of anisole (3a), the cyclodextrins also limit the extent of formation of the dibromide (6a), and again it is α-cyclodextrin that has the most effect. It seems likely that this is mainly due to the cyclodextrins retarding further bromination of the monobromide (5a), by blocking the 2-position. The net result of these effects is an increase in the yields of the monobromides (5a,b), from 73 to 94, and 55 to 98%, respectively, and a substantial decrease in the quantity of the corresponding by-products, from 27 to 6, and 45 to 2%.

Table 1. Products of bromination of compounds (3a–c) and (7a,b)[A]

Entry	Substrate	Cyclodextrin (CD)	Reagent (mol. equiv.)	Product Ratios (%)					
				(3)	(4)	(5)	(6)		
1	(3a)	–	1.1	0	12	73	15		
2		α-CD	1.1	0	2	94	4		
3		β-CD	1.1	0	6	86	8		
4	(3b)	–	1.1	0	42	55	3		
5		α-CD	1.1	0	0	98	2		
6		β-CD	1.1	0	21	79	0		
7	(3c)	–	1.1	41	2	57	0		
8		α-CD	1.1	40	2	58	0		
9		β-CD	1.1	77	1	22	0		
				(7)	(9)	(11)	(13)	(14)	
10	(7a)	–	0.6	50	23	12	14	1	
11		α-CD	0.6	40	42	8	9	1	
12		β-CD	0.6	36	59	3	2	0	
13	(7a)	–	1.1	23	37	19	20	1	
14		α-CD	1.1	12	46	18	21	1	
15		β-CD	1.1	4	86	5	5	0	
16	(7a)	–	2.2	0	30	29	34	7	
				(7)	(9)	(11)	(13)	(14)	(X)
17	(7b)	–	0.6	51	36	8	5	0	0
18		α-CD	0.6	43	48	6	3	0	0
19		β-CD	0.6	44	48	5	3	0	0
20	(7b)	–	1.1	12	39	9	7	20	13
21		α-CD	1.1	5	64	9	6	13	3
22		β-CD	1.1	3	72	7	4	1	13

[A] Reaction with pyridinium dichlorobromate in water at room temperature. Reaction time was 1 h for (3a,b) and (7a,b) and 16 h for (3c).

Table 2. NMR signals used for determining product ratios

Compound	Solvent	Spectral Data[A]	Ref
(3a)	$CDCl_3$	7.22 (2H, m, H3, H5), 6.91–6.80 (3H, m, H2, H4, H6), 3.77 (3H, s, OCH_3)	
(3b)	d_6-DMSO	7.54 (2H, d, *J* 7.5 Hz, H2, H6), 7.26 (2H, t, *J* 7.5 Hz, H3, H5), 7.00 (1H, t, *J* 7.5 Hz, H4), 2.02 (3H, s, $NHCOCH_3$)	
(3c)	$CDCl_3$	7.38 (2H, m, H3, H5), 7.24 (1H, m, H4), 7.09 (2H, m, H2, H6), 2.28 (3H, s, $COCH_3$)	
(4a)	$CDCl_3$	7.54 (1H, dd, *J* 8.0, 1.5 Hz, H6), 7.27 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, H5), 6.90 (1H, dd, *J* 8.5, 1.5 Hz, H3), 6.84 (1H, ddd, *J* 8.5, 7.5, 1.5 Hz, H4), 3.89 (3H, s, OCH_3)	
(4b)	d_6-DMSO	7.61 (1H, d, *J* 7.5, 1.5 Hz, H6), 7.33 (1H, td, *J* 7.5, 1.5 Hz, H5), 7.10 (1H, td, *J* 7.5, 1.5 Hz, H4), 2.06 (3H, s, $NHCOCH_3$)	[
(4c)	$CDCl_3$	7.60 (1H, dd, *J* 8.5, 1.5 Hz, H6), 7.32 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, H5), 7.13 (1H, m, H3), 7.12 (1H, m, H4), 2.34 (3H, s, $COCH_3$)	[
(5a)	$CDCl_3$	6.70 (2H, d, *J* 9.0 Hz, H2, H6), 7.29 (2H, d, *J* 9.0 Hz, H3, H5), 3.79 (3H, s, OCH_3)	
(5b)	d_6-DMSO	7.53 (2H, d, *J* 9.0 Hz, H3, H5), 7.43 (2H, d, *J* 9.0 Hz, H2, H6), 2.02 (3H, s, $NHCOCH_3$)	
(5c)	$CDCl_3$	7.46 (2H, d, *J* 9.0 Hz, H3, H5), 6.96 (2H, d, *J* 9.0 Hz, H2, H6), 2.27 (3H, s, $COCH_3$)	[
(6a)	$CDCl_3$	7.65 (1H, d, *J* 2.5 Hz, H3), 3.87 (3H, s, OCH_3)	[
(6b)	d_6-DMSO	7.72 (1H, d, *J* 2.1 Hz, H3), 2.11 (3H, s, $NHCOCH_3$)	[
(7a)	CD_3OD	7.11 (1H, t, *J* 8.0 Hz, H5), 6.71 (2H, m, H4, H6), 6.66 (1H, m, H2), 3.73 (3H, s, OCH_3), 2.28 (3H, s, $ArCH_3$)	
(7b)	CD_3OD	7.35 (1H, br s, H2), 6.90 (1H, br d, *J* 8.0 Hz, H4), 7.15 (1H, t, *J* 8.0 Hz, H5), 7.30 (1H, br d, *J* 8.0 Hz, H6)	
(9a)	CD_3OD	7.35 (1H, d, *J* 8.5 Hz, H5), 6.83 (1H, d, *J* 3.0 Hz, H2), 6.63 (1H, dd, *J* 8.5, 3.0 Hz, H6), 3.74 (3H, s, OCH_3), 2.32 (3H, s, $ArCH_3$)	[
(9b)	CD_3OD	7.47 (1H, d, *J* 2.5 Hz, H2), 7.41 (1H, d, *J* 8.5 Hz, H5), 7.28 (1H, dd, *J* 8.5, 2.5 Hz, H6)	[
(11a)	CD_3OD	7.49 (1H, d, *J* 9.0 Hz, H5), 6.80 (1H, d, *J* 9.0 Hz, H6)	
(11b)	CD_3OD	7.53 (1H, d, *J* 8.5 Hz, H5)	[
(13a)	CD_3OD	7.60 (1H, s, H6), 6.69 (1H, s, H3)	
(13b)	CD_3OD	7.60 (1H, br s, H6), 7.76 (1H, s, H3)	[
(14a)	CD_3OD	7.79 (1H, s, H5)	
(14b)	CD_3OD	7.87 (1H, s, H5)	[
(X)	CD_3OD	7.12 (1H, ddq, *J* 8.5, 3.0, 0.5 Hz), 7.68 (1H, d, *J* 8.5 Hz)	

[A] Discrete signals were not observed for all resonances; those which could not be unambiguously assigned are not shown.
[B] Spectrum of an authentic sample.

The cyclodextrins do not alter the regioselectivity of bromination of phenyl acetate (3c), although β-cyclodextrin decreases the extent of reaction (Table 1, entries 7–9). In the reactions of the methylanisole (7a) and methylacetanilide (7b), the cyclodextrins increase the yields of the monobromides (9a,b), probably by limiting the subsequent reactions of (9a,b) to give the dibromides (11a,b) and (13a,b), and tribromides (14a,b), as well as by decreasing the extent of reaction *via* the monobromides (8a,b), (10a,b) and (12a,b), to give (11a,b), (13a,b) and (14a,b). Again the effect of the cyclodextrins is to prevent bromination adjacent to the methoxy and acetamido groups, in a similar manner to that seen with anisole (3a) and acetanilide (3b), but in the methylated systems β-cyclodextrin has the greatest effect. When 1.1 mol. equiv. of the brominating agent was used with β-cyclodextrin, the yields of the monobromides (9a,b), increased from 37 to 86, and 39 to 72%, respectively, and there was a substantial decrease in the quantity of the corresponding by-products, from 63 to 14, and 61 to 28%.

It is not obvious why α-cyclodextrin has the greatest effect on the bromination of anisole (3a) and acetanilide (3b), yet the reactions of the methylated substrates (7a) and (7b) are most affected by β-cyclodextrin. The outcomes will depend on the extent of inclusion of the reagent, pyridinium dichlorobromate, as well as the substrates (3a,b) and (7a,b), and the relatively reactivity of the free and included species. The systems are further complicated by possible complexation of the primary products such as the monobromides (8a,b), (9a,b) and (10a,b), affecting their subsequent reactions. Nevertheless, it seems likely that a major contributing factor to the regiocontrol provided by the cyclodextrins derives from complexation of the substrates (3a,b) and (7a,b) in such a way as to restrict access of the reagent adjacent to the methoxy and acetamido substituents. Such shielding is reflected in ROESY

spectra of mixtures of anisole (3a) and α- and β-cyclodextrin (Figures 1 and 2, respectively), which both show NOEs between the resonances of the *ortho* hydrogens of the substrate (3a) and the cyclodextrin C3-H and C5-H resonances.

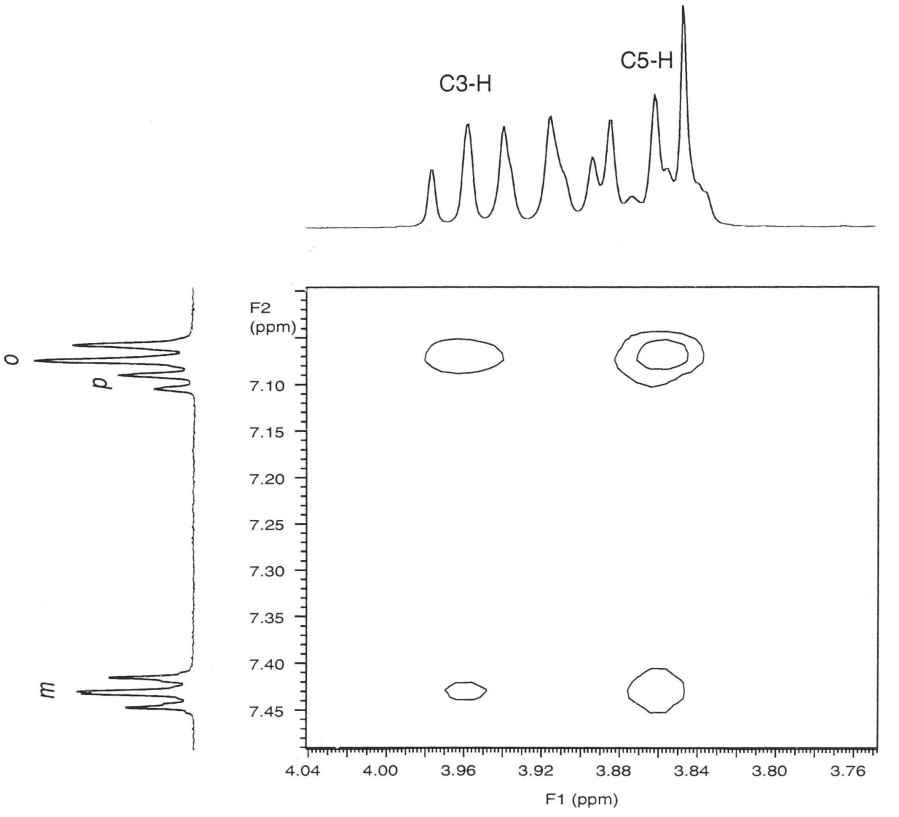


Fig. 1. A portion of the ROESY spectrum (500 MHz) recorded of a solution of anisole (3a) (10 mM) and α-cyclodextrin (10 mM) in D_2O, showing interactions between resonances of the cyclodextrin (x-axis) and those of the anisole (3a) (y-axis).

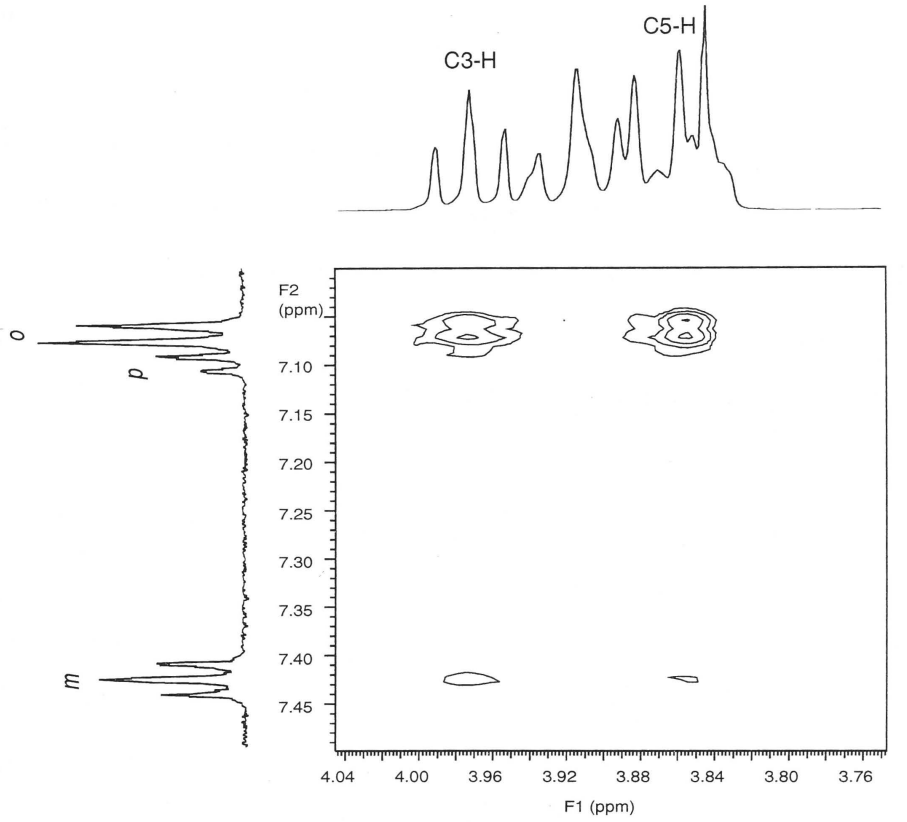


Fig. 2. A portion of the ROESY spectrum (500 MHz) recorded of a solution of anisole (3a) (2 mM) and β-cyclodextrin (2 mM) in D_2O, showing interactions between resonances of the cyclodextrin (x-axis) and those of the anisole (3a) (y-axis).

In summary, both α- and β-cyclodextrin affect the regioselectivity of bromination of anisole (3a) and acetanilide (3b) and the methylated analogues (7a,b), to increase the yields of the corresponding bromides (4a,b) and (9a,b). A corollary of this is that the reactions are further improved by the substantial reductions in the yields of the by-products. Since the brominations occur readily in water at ambient temperature, and they require only stoichiometric quantities of reagents, the cyclodextrins make them very efficient chemical transformations.

Experimental

General

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian Inova 500 spectrometer or a Varian Gemini 300 spectrometer. Spectra were referenced against tetramethylsilane (δ 0.00 ppm) for $CDCl_3$ solutions, external 3-(trimethylsilyl)-3,3,2,2-tetradeuteropropionic acid sodium salt for D_2O solutions, or residual protons for other deuterated solvents. ROESY spectra were recorded on a Varian Inova 500 spectrometer employing a mixing time of 250 ms. The sample tubes were sealed with RotoTite® valves purchased from Wilmad Glass, and samples were repeatedly degassed by freeze-pump-thaw cycling before spectra were recorded. The samples contained either α-cyclodextrin (0.01 M) and anisole (3a) (0.01 M), or β-cyclodextrin (0.002 M) and anisole (3a) (0.002 M), in D_2O.

α-Cyclodextrin and β-cyclodextrin were generous gifts of Nihon Shokuhin Kako Co., Japan. They were recrystallised from water and dried *in vacuo* over P_2O_5 to constant weight before use. Water was purified with a MilliQ-Reagent water system.

Anisole (3a), phenyl acetate (3c), 4-bromoanisole (5a), 4-bromoacetanilide (5b), 3–methylanisole (7a) and *m*-toluidine were purchased from Sigma-Aldrich Chemical Company. Acetanilide (3b) was bought from Ajax Chemicals and 2-bromoanisole (4a) was purchased from Fluka Chemical Company Ltd. Pyridinium dichlorobromate was prepared as described by Muathen.[18] Anisole (3a) was purified by distillation (bp 153–154 °C) before use. 3-Methylacetanilide (7b) was prepared by acetylating *m*-toluidine.(ref 27) Samples of 2,4-dibromo-3-methylanisole (11a), 2,4-dibromo-5-methylanisole (13a) and 2,4,6-tribromo-3-methylanisole (14a) were prepared by bromination of 3-methylanisole (7a) with bromine in acetic acid.[28]

General bromination procedure

The aromatic substrate (3a–c) or (7a,b) (0.2 mmol) in methanol (1.5 mL) was added to water (100 mL) that contained either no cyclodextrin or α- or β-cyclodextrin (2.0 mmol), and the resulting mixture was stirred vigorously. Pyridinium dichlorobromate (0.22 mmol) was added and the total volume of the solution was made up to 150 mL with water. The resulting mixture was stirred at room temperature, for 1 h in the cases of (3a,b) and (7a,b), and 16 h with (3c), then the reaction was quenched through the addition of an excess of $NaHSO_3$. The solution was extracted with ether (2 × 80 mL), and the ether extracts were washed with water (100 mL), dried and concentrated under

reduced pressure. The residue was analysed using ^{1}H NMR spectroscopy. Spectra were recorded in either $CDCl_3$, CD_3OD or d_6-DMSO, depending on the solubility of the components. The ratios of the components present are shown in Table 1, as determined by integration of key resonances that are listed in Table 2.

Acknowledgement

The authors gratefully acknowledge the support of the Australian Research Council and the award of an APA(I) Scholarship to P.G.D.

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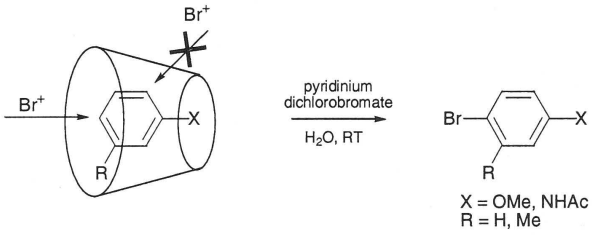
Graphical Abstract



Cyclodextrins act as molecular reactors to change the ratios of the products of reactions of anisole, 3-methylanisole, acetanilide and 3-methylacetanilide with pyridinium dichlorobromate. Yields of the substituted products are increased and the quantities of by-products formed are substantially reduced.